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DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC CONSIDERATIONS IN PRIMARY PULMONARY HYPERTENSION

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II: DEDICATION

To Eileen, Sarah, Mark and Ruth.

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IV: CONTENTS

V: ABSTRACT

The diagnosis of primary pulmonary hypertension (PPH) and prediction of its course, whether treated or untreated, presents several problems. These are of particular relevance when selection of patients for, and timing of heart-lung transplantation is being considered.

I performed a retrospective study on patients with PPH and chronic large vessel thromboembolic pulmonary hypertension (TPH) seen at Groote Schuur Hospital between 1957 and 1985 in an attempt to:

1. Establish the diagnostic and prognostic value of clinical features, lung function tests, cardiac catheterisation, isotope lung scans and, in the PPH group, response to therapy;

2. Review our experience of the effects of treatment with vasodilators and oral anticoagulants, and the results of heart and lung transplantation in the PPH group;

3. Attempt to identify features which could be used to predict prognosis in PPH; and thereby

4. Define criteria for selecting PPH patients whose prognosis could be improved by heart-lung transplantation.

Where possible patients were recalled for assessment. 38 patients with PPH and 16 with TPH were studied. All patients with total lung capacity, forced vital capacity or forced expiratory volume in 1 second to forced vital capacity ratio less than 2/3 predicted were excluded.

The PPH patients were younger than those with TPH. A preponderance of females was present in both groups. Raynaud's phenomenon occurred significantly more frequently in the PPH group. The higher prevalence of a right ventricular fourth heart sound in this group could not be explained and may have been a chance occurrence. Electrocardiographic evidence of right axis deviation and right ventricular hypertrophy occurred more frequently. Mean total lung capacity was considerably below predicted and significantly lower than in the TPH group.

Mean pulmonary artery pressure was significantly higher in the PPH group. A greater degree of ventilation/perfusion mismatching in the TPH patients was suggested by the significantly lower mean systemic arterial oxygen saturation.

Normal or low probability radionuclide lung scans were found in all cases with PPH, while all TPH patients had high probability scans.

Stage I exercise studies performed in 4 PPH patients at diagnosis showed significant limitation of effort tolerance, but there was no correlation between performance and several resting haemodynamic variables.

Retrospective analysis failed to identify features that identified PPH patients likely to respond to vasodilator therapy. Long term vasodilator administration appeared to be effective in only 2 of 6 patients.

54% survived 40 months from the onset of symptoms. Electrocardiographic evidence of right ventricular hypertrophy occurred less frequently in the long survival group (40 months or more from diagnosis). This group also had a lower mean pulmonary artery pressure than the short survival group (12 months or less from diagnosis). Neither mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, mean right atrial pressure, systemic arterial oxygen saturation nor systemic vascular resistance were directly related to survival in the short and long survival groups. No correlation was found between the pulmonary artery pressure and the severity of the histological changes.

The prognosis of PPH patients treated conservatively appears to be better than originally reported. Heart-lung transplantation should be considered for patients with severe pulmonary hypertension or in the terminal phases of progressive disease.

VI: INTRODUCTION

Historical Background

Primary pulmonary hypertension (PPH) was first described as a pathological entity in the late nineteenth and early twentieth century.[72,96] In 1935 Brenner correlated the clinical picture with the histopathological findings.[7] The first clinical description including catheterization data was published in 1951 by Dresdale and his coworkers.[29] In 1970 Wagenvoort and Wagenvoort defined criteria for the various histopathological patterns found in these patients.[122] A World Health Organization meeting in 1973 reviewed the information regarding the pathogenesis, pathophysiology, clinical patterns, epidemiology, morphology and nomenclature of this condition.[42] The areas for further study which were identified at this meeting have guided much of the subsequent research in this field.

Nomenclature

The term "primary pulmonary hypertension" has been used in two quite separate ways: it has been used by the clinician to indicate the presence of an elevated pulmonary arterial pressure in the absence of a discernible cause whereas the pathologist has used it to imply a distinct histological pattern characterized by concentric intimal fibrosis, necrotizing arteritis, plexiform lesions and other associated features with no pathological evidence as to the cause of these changes. The WHO report suggested that the term "plexogenic pulmonary arteriopathy" be used to describe this specific histological entity and that the term "primary pulmonary hypertension" be restricted to usage in a clinical sense to imply pulmonary hypertension for which clinical investigations fail to reveal a cause. This clinical category includes 3 distinct histopathological patterns:

(a) plexogenic pulmonary arteriopathy;[21,122]

(b) pulmonary veno-occlusive disease (PVOD) in which there is widespread occlusion of pulmonary veins and venules[109,118]; or

(c) recurrent pulmonary microthromboembolism[31,122].

Although it is now possible in some instances to recognize PVOD and TPH during life there are other cases where even after full clinical investigation it is still impossible to differentiate the condition from plexogenic pulmonary arteriopathy. Only these cases would be included in the category of primary pulmonary hypertension.

Aims

The aims of the present study were:

(1) To analyze the features of patients seen at Groote Schuur Hospital with primary pulmonary hypertension and to compare them with those with chronic large vessel thromboembolic pulmonary hypertension;

(2) To evaluate the prognosis of the patients in these two groups;

(3) To assess the effect of treatment with anticoagulants, vasodilators and heart-lung transplantation in the primary pulmonary hypertension group; and

(4) To attempt to identify factors predictive of prognosis in primary pulmonary hypertension and thereby to define criteria for patient selection for heart-lung transplantation.

Diagnostic criteria:.

We define primary pulmonary hypertension clinically as pulmonary hypertension (mean pulmonary artery pressure 25 mmHg or greater at rest with pulmonary capillary wedge or left atrial pressure 15 mmHg or less) with no clinical, cardiac catheterization or pulmonary angiographic evidence of congenital heart disease, pulmonary artery thromboembolic lesions, pulmonary veno-occlusive disease or significant disturbances in ventilation (total lung capacity, forced vital capacity or ratio of FEV_1 to FVC less than $^2/_3$ predicted). This definition excludes such diseases as mitral stenosis, left atrial tumours, clinically demonstrable pulmonary venous disease, left ventricular dysfunction or severe restrictive or obstructive lung disease. Significant restriction of pulmonary volumes has been reported in patients with primary or chronic thromboembolic pulmonary hypertension with no evidence of interstitial lung disease.[9,47] I nevertheless chose to exclude patients with significant abnormalities in lung function to ensure that no patient with pulmonary hypertension aggravated by coexisting lung disease was included in this study.

VII: METHODS

Thirty-eight patients with primary pulmonary hypertension who were seen between 1957 and 1985 at Groote Schuur Hospital were reviewed. Sixteen patients with chronic pulmonary hypertension due to thromboembolism involving large and medium sized pulmonary arteries who presented during the same period were also reviewed in order to enable comparison of the clinical features at presentation and subsequent course of the disease process in the two groups. Patients were identified by means of the hospital computer retrieval system and the records of the cardiac and respiratory clinics. All those who met the defined diagnostic criteria were included. These patient groups necessarily included patients investigated to differing degrees as certain investigations only became available during the later years of the study.

Clinical features at the time of diagnosis were obtained from the patients' clinical notes. The onset of the disease was defined as the time of the first symptom. Chest radiographs, radioisotope lung scans and pulmonary histology were reviewed where possible. Failing this, the formal reports issued at the time of investigation were used. Haemodynamic and pulmonary angiographic data were obtained from the original reports. In those patients in whom pulmonary function tests were performed, forced vital capacity (FVC), total lung capacity (TLC) by helium dilution method, single breath gas transfer for carbon monoxide (TLCO SB) and KCO (gas transfer per litre lung volume) were measured using standard equipment

and methods. The results were corrected to BTPS and expressed as a percentage of predicted value for sex, age and height.[20,40,108] Forced expiratory volume in 1 second (FEV_1) was expressed as a percentage of FVC.

Radionuclide perfusion lung scans were performed on 19 patients using 4 mCi of 99m-technetium labelled macroaggregated human albumin imaged in 4 views with a gamma camera. Where these showed abnormalities 2 further views in the right and left lateral positions were done. Ventilation scans were performed in which an 81m-krypton and air mixture was breathed at tidal volumes. Where possible the scans were reviewed. In other cases we used the report issued at the time of the investigation. Abnormal scans were interpreted as showing a high or low probability of pulmonary embolism. A high probability (HP) scan showed multiple lobar or segmental perfusion defects without ventilation abnormality while multiple subsegmental (patchy) perfusion defects were interpreted as a low probability (LP) scan.

Pulmonary haemodynamics and acute response to vasodilator therapy were evaluated either during a full study in the cardiac catheterization laboratory or by means of right heart catheterization in the respiratory intensive care unit. A change greater than 10% of the resting baseline haemodynamic parameters was considered significant.

Pulmonary angiography was performed by members of the Cardiac Clinic, Groote Schuur Hospital and their reports form the

basis of our evaluation. Complete or partial obstruction of a main or several lobar pulmonary arteries was considered diagnostic of pulmonary embolic disease. The absence of large vessel obstruction or strictures and the occlusion of small peripheral vessels was taken to indicate a diagnosis of PPH.

Stage 1 maximal exercise testing was performed on five patients using the method of Jones and Campbell.[53] Of the four patients who had been tested at the time of diagnosis three were recalled for re-testing together with a fifth patient who had not been tested at the time of her initial diagnosis.

Follow up information was obtained from the clinical notes and, where they were incomplete, attempts were made to contact the patients themselves, their families, or their attending doctors by letter, telephone or personal visit. Four PPH patients (the only survivors resident in Cape Town) were recalled for clinical re-evaluation, chest X-ray, pulmonary function tests and stage 1 exercise studies. Only those patients who had adequate follow up information (to death or for forty months from the onset of symptoms) were included in the analysis of survival.

All patients who had undergone cardiac catheterization and who had been adequately followed up (to death or for 40 months or more from the time of catheterization) were categorized into two groups: Group 1 (7 patients) who died

within 12 months of catheterization and Group 2 (7 patients) who survived for 40 months or longer after catheterization. The characteristic features of the two groups were evaluated and compared.

The histological features of lung biopsy or autopsy specimens were reviewed where possible.

Differences between groups were assessed by means of Mann-Whitney U test and Fisher's exact test. The survival time in the short and long survival groups was examined in relation to measured haemodynamic data at the time of initial assessment by means of Spearman's rank correlation coefficient. Statistical significance was taken as $p<0.05$.

VIII: RESULTS

VIII A: Demographic and Pathogenetic Features

Table VIII A(i): Demographic data of patients studied.

	PPH	TPH	P
Number of patients	38	16	
Age (years)	33.7±13.4*	45.7±12.0*	<0.05
Symptom duration before diagnosed (months)	27.1±47.3*	14.8±13.0*	
Males	34%	31%	
Females	66%	69%	
Black	8%	12%	
White	47%	25%	
Mixed Race	45%	63%	
Associated connective tissue disease	16%	0%	
Smoking	52%	43%	
Previously pregnant	79%	100%	
Number of pregnancies	2.8±2.7*	5.9±3.7*	<0.05
Oral contraceptive	29%	20%	

* = mean ± standard deviation
% = percentage of group

PPH is an uncommon condition. McDonnell noted a prevalence of 0.13% in a series of autopsied patients greater than 1 year of age.(70) By 1977 one thousand cases had been reported.(121) Paul Wood reported a frequency of 17 among 10,000 consecutive cases seen by him with cardiovascular disease of all types.(132)

We traced 38 patients seen at this hospital between 1957 and 1985. As diagnostic approaches and available facilities varied during this period the patients were investigated to differing degrees. The diagnosis in the 38 PPH patients was made as follows:

Lung histology (heart-lung transplantation):	1
Autopsy:	4
Pulmonary angiography and subsequent autopsy:	1
Pulmonary angiography:	23
Clinical picture with elevated pulmonary artery pressure at cardiac catheterisation:	3
Family history of angiographically demonstrated PPH, clinical picture and elevated pulmonary artery pressure:	2
Clinical picture of PPH with systemic lupus erythematosus or systemic sclerosis and no evidence of interstitial lung disease on chest radiograph or pulmonary function testing:	4

An accurate estimation of the true frequency of the condition has been hampered in the past by the non-specific symptoms of the disease and by the lack of a simple screening test for pulmonary hypertension. The recent advent of a newly developed non-invasive technique for assessing pulmonary artery pressure will be of great benefit in future studies.[21]

The preponderance of young females in our group of adult patients accords with the observation by other authors that both the sporadic and familial forms of PPH particularly affect young women, although neither men nor other age groups are exempt.[39,65,93,99,121,123] This has prompted speculation that female hormones or pregnancy-related changes may contribute to the pathogenesis of this condition. Kleiger and his colleagues[56] reported 6 young women who developed pulmonary hypertension after taking oral contraceptives for periods from 6 months to 5 years. Three of the women had no known predisposition to pulmonary hypertension while of the remaining 3 one had a corrected patent ductus arteriosus, one had a family history of pulmonary hypertension and one had systemic lupus erythematosus. Oakley and Somerville[80] reported 3 patients with congenital left to right shunts who developed severe pulmonary hypertension and shunt reversal 6 months to 2 years following the commencement of oral contraceptive therapy. Postmortem examination of the patients who died in these 2 series revealed intimal proliferation, medial hypertrophy and, in one, angiomatoid lesions with no evidence of

thromboemboli in the pulmonary vasculature. Irey and Norris[51] reported 16 women who developed intimal vascular proliferation in numerous sites while under the influence of female hormones (5 were pregnant, 4 postpartum and 7 were taking oral contraceptives). No evidence of a primary thrombotic aetiology was found nor were similar intimal proliferative changes noted in a control group who were neither pregnant nor receiving oral contraceptives.

Although normal pregnant women have a lower pulmonary vascular resistance than non-pregnant women[127,128], a study in cattle has shown that pulmonary vascular resistance increases during pregnancy in a specific subgroup of cattle which are susceptible to developing pulmonary hypertension and right heart failure at high altitude. This does not occur in other cattle[73]. This supports the postulate that pregnancy or oral contraceptives may cause or accelerate the development of pulmonary hypertension in certain predisposed individuals. In this study, however, only 29% of the women used oral contraceptives while 79% had had a prior pregnancy. These findings are similar to those of Fuster et al and are not significantly different from what may be found in a normal female population of the same age range[39].

Raynaud's phenomenon and connective tissue diseases have been reported in 7 to 30% of patients with primary pulmonary hypertension[122,123]. Scleroderma, particularly the CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangectasia) variant, systemic lupus

erythematosus and rheumatoid arthritis have been reported[14,55,77,82,104,105]. In addition a man with dermatomyositis and pulmonary hypertension with no radiographic evidence of interstitial fibrosis but moderate restriction on spirometry has been reported[11]. Connective tissue diseases occurred in 16% of our patients (CREST variant of scleroderma 2; systemic lupus erythematosus 3; juvenile chronic arthritis 1). The frequent occurrence of Raynaud's phenomenon and connective tissue diseases with PPH has led to a postulate that autoimmunity might play a major role in the aetiology. However, there is only one report of an autoimmune mechanism in PPH: the finding of immune complexes in the small pulmonary blood vessels of a patient with pulmonary veno-occlusive disease[19]. The lack of response to corticosteroids or to a combination of prednisone and azathiaprine provides further indirect evidence against a major role of immunological mechanisms[24]. Wagenvoort contests the hypothesis that a pulmonary vasculitis due to an allergic drug reaction or polyarteritis nodosa may result in PPH[121, 122]. In his series evidence of pulmonary arteritis and fibrinoid necrosis only occurred in such patients when their pulmonary vessels showed histological evidence of longstanding severe pulmonary hypertension, suggesting that pulmonary hypertension preceded and precipitated the arteritis rather than resulted from it.

The pulmonary vascular changes may merely be one expression of a generalized mechanism for progressive vascular damage. Wood suggested that vasoconstrictive factors may play a

part[133]. Increased vascular tone is thought to be the initial factor[31].

In primary Raynaud's phenomenon cold stimulation can cause a reduction in size of the pulmonary capillary bed[35]. This is probably effected by precapillary vasoconstriction. In scleroderma the intimal changes in digital, renal and pulmonary arteries are similar in some respects[95]. Acute and chronic constriction of interlobular renal arteries with lumina previously narrowed by intimal hyperplasia has been suggested as the mechanism underlying the rapid onset of the malignant hypertension and renal failure seen in scleroderma renal crisis[13]. Further evidence to support this theory has been provided by reports of the successful treatment of this syndrome with modern vasodilator therapy[15,71]. In experimental animals intense pulmonary artery vasospasm has been shown to result in medial hypertrophy, fibrinoid necrosis, pulmonary arteritis and occasional plexiform lesions[172].

The association of liver disease with pulmonary hypertension was first noted in 1951[68]. Initial doubts that this association was no more than coincidental were disproved by McDonnell et al who showed a prevalence of PPH of Ø.73% among autopsied patients with cirrhosis compared to a prevalence of Ø.13% among all autopsies[7Ø]. A significant difference in prevalence was also noted in their clinical series. Pulmonary hypertension can affect patients with portal hypertension of any cause. In our series one patient had

chronic active hepatitis and a marked portal-systemic shunt. Another patient who at 32 developed symptoms referable to pulmonary hypertension had had portal vein obstruction since early childhood. This was thought to be due to angiomatous malformation of the vein or sepsis of the umbilical cord. Portal hypertension is an essential feature of the association and always precedes the development of pulmonary hypertension[62]. The interval between the first manifestation of portal hypertension and the first manifestation of pulmonary hypertension in this patient was exceptionally long, the usual interval being 2 to 15 years. The presence of portal-systemic shunting (spontaneous or surgically created) favours the development of pulmonary hypertension[62]. Some authors have attributed the pulmonary hypertension to microemboli arising from the portal venous territory[76]. However, the histological features in these patients are regarded as incompatible with chronic pulmonary embolism. In addition, the prevalence of pulmonary hypertension is not higher in patients with, than in patients without, thrombosis of the portal vein, which would be expected if pulmonary hypertension were the consequence of microemboli[62]. It is more probable that the pulmonary hypertension results from the effect of a vasoconstrictive agent or a substance toxic to the walls of the small pulmonary arteries that is produced in the splanchnic territory, destroyed by the liver in normal subjects, but which reaches the pulmonary arteries through portal-systemic shunts[62,70].

This mechanism is comparable to that postulated in the pathogenesis of dietary pulmonary hypertension where it has been suggested that toxic compounds taken in food, beverages or medicines are released from the gut, pass through the liver and finally reach and injure pulmonary arteries. Alkaloids from the genus Crotalaria and the genus Senecio have produced hepatic necrosis and pulmonary hypertension in monkeys and rats. However, despite widespread use of these plants in herbal remedies and bush teas there has been only one report of a possible association between Crotalaria laburnoides ingestion and PPH in man[41]. While Crotalaria intoxication causing veno-occlusive disease of the liver has been well described in Jamaican children, none of the patients had evidence of pulmonary vascular disease[5,6]. The relationship between the ingestion of these substances and the development of pulmonary hypertension in man has thus yet to be proven.

Iatrogenic pulmonary hypertension has been reported in association with 3 pharmacological agents. Several cases have been associated with the use of phenformin[36]. These have improved on discontinuation of the drug. Between 1966 and 1968 a marked increase in the incidence of PPH was noted in Switzerland, Austria and, to a lesser extent, West Germany[121]. The histological picture was that of plexogenic pulmonary arteriopathy. Because of a temporal and geographical association between this outbreak and the distribution of a new appetite suppressing drug, aminorex fumarate, and because 80% of the patients reported using this

agent, a causal relationship was accepted. The epidemic subsided within 4 years of the withdrawal of the drug. More recently another appetite suppressant, fenfluramine, has been associated with 2 cases of PPH which improved when the drug was withdrawn.[28] None of our patients gave a history of exposure to any of these substances.

The possibility that certain cases of PPH are familial was first suggested in 1927 when two sisters with pulmonary atherosclerosis of unknown origin were described by Clarke et al[17]. The mode of inheritance was initially postulated by Hood and his colleagues to be autosomal recessive with incomplete male penetrance[46]. Subsequent studies have provided evidence for an autosomal dominant pattern of inheritance with varying penetrance[65]. Loyd and his colleagues described 52 known patients in 14 families and at least 9 additional persons who transmitted the gene but who are without apparent disease. They cite a case of father to son transmission as evidence against an X-linked mode of transmission. The infrequent expression of the gene in some families remains unexplained. Many cases previously labelled as sporadic may well prove to be familial when a more extensive family history is obtained. Three families were included in our study. In the first, two cousins (one male, one female) were affected. The female cousin gave a history of pulmonary hypertension in 2 of her 3 sisters. Two brothers in the second family developed symptoms in early adolescence and died within 2 years. An older sister and younger brother were unaffected. In the third family a

mother and her daughter developed the condition. Two other children were unaffected. Survival of cases of familial PPH is similar to that of the sporadic form[65]. The pathogenesis in these cases is uncertain. A defect in fibrinolytic activity has been noted in one affected family[50].

It has been suggested that the hypercoagulable state attributable to the lupus anticoagulant and associated anticardiolipin antibodies plays a causative role in the genesis of PPH[2]. Anticardiolipin antibodies were noted in 3 of 10 patients reported by Sleeper[113] and in 2 of 23 in a second series[123]. Asherson et al detected the lupus anticoagulant in 5 of 6 patients with systemic lupus erythematosis and pulmonary hypertension[2].

Pulmonary hypertension due to widespread obliterative arteriolitis secondary to the deposition of schistosomal ova occurs in 2.1% of all cases of bilharzia[110]. Although some of our patients came from areas where bilharzia is endemic, none gave a history or showed features of infection, and no ova were found in those patients whose lung tissue was examined histologically.

Thromboembolism has been suspected to play a significant causative role in PPH[122]. Obstruction of the muscular pulmonary arteries and arterioles rather than the larger elastic ones is the form of recurrent thromboembolism that clinically appears as PPH[31,39,122]. It is characterized by

an insidious onset with a relentless course of progressive dyspnoea and is quite unlike the presentation of patients with recurrent embolism to large pulmonary arteries. Such patients tend to have a step-like clinical course with acute exacerbations of dyspnoea and chest pain with intervening periods during which effort tolerance remains reasonably stable[83]. Our study confirms previous reports that patients with chronic large vessel thromboembolic disease tend to be older than those with PPH. The mean ages (with ranges) of 46(28 to 73) and 34 (13 to 58) years respectively were almost identical to those noted in previous studies.

The long duration of symptoms before diagnosis in the PPH group is in accord with previous studies[3,39,123] and suggests that the disease process was well advanced before the diagnosis was made. Early diagnosis is difficult to achieve where the initial symptoms are relatively non-specific. The trend towards a shorter duration of symptoms before diagnosis in the large vessel TPH group was not significant.

Two patients in the TPH group were at high risk of developing thromboembolic disease: one had polycythaemia rubra vera while the other was deficient in anti-thrombin III. No such risk factors were present in the PPH group.

VIII B: Clinical Features:

VIII B(i): Symptoms and Signs:

Table VIII B(i): Symptoms and signs of patients studied:

	PPH	TPH	P
Number	38	16	
Dyspnoea on exertion	88%	93%	
Severity of dyspnoea (NYHA Classification)	2.7±0.8*	2.6±0.6*	
Chest pain	32%	25%	
Vertigo or syncope	43%	20%	
Cough	36%	38%	
Fatigue	40%	31%	
Raynaud's phenomenon	22%	0%	<0.05
Arthritis	13%	0%	
Elevated JVP	51%	56%	
Mean JVP	3.7±3.6*	4.9±4.8*	
Accentuated P_2	97%	100%	
RV Heave	87%	75%	
Tricuspid incompetence	32%	38%	
Pulmonary incompetence	13%	19%	
Right ventricular third heart sound	26%	38%	
Right ventricular fourth heart sound	32%	0%	<0.01
Hepatomegaly	40%	38%	
Splenomegaly	8%	6%	
Cyanosis	16%	31%	
Lower extremity oedema	24%	44%	
Lower extremity varicosities	3%	31%	<0.01

* = mean ± SD
% = percentage of group

Dyspnoea on exertion was the most frequent symptom, occurring in 88% of the PPH patients. These had a mean NYHA grading of 2.7±Ø.8 (mean ± SD). Forty-three per cent complained of vertigo or syncope. This appears to result from diminished cerebral blood flow due to an inability to increase cardiac output during exertion because of a fixed high pulmonary resistance[29]. The anginal chest pain that occurred in 32% of our patients has been ascribed to right ventricular subendocardial ischaemia secondary to hypoperfusion of hypertrophied myocardium and a diminished perfusion gradient resulting from elevated right ventricular wall tension[112]. The association of Raynaud's phenomenon with PPH (as discussed in section VIII A) occurred in 22% of our patients. The symptoms experienced by our patients are similar to those reported by other authors.[23,48,113,123] Raynaud's phenomenon and arthritis were not noted in the TPH group, but they were similar to the PPH patients in other respects.

The most frequently observed clinical sign in the PPH group was accentuation of the pulmonary component of the second heart sound. This was observed in all but one (97%) of our patients. However this was not a blinded study and the accuracy and independence of this observation from other signs cannot be assessed from this study. The other features as outlined in Table VIII B(i) are similar to those found in previous studies.[23,113,123] The clinical findings in the TPH group differed in two respects only: there was a higher incidence of lower extremity varicose veins ($p<Ø.Ø1$)

and in none of the TPH patients was a right ventricular fourth sound noted ($p<0.01$). The last finding was not noted in previous studies[3,23] and as no reason for this is apparent it is probably a chance finding due to the potential for error implicit in retrospective documentation of the observations of a large number of physicians.

VIII B(ii): Chest radiographic features:

Table VIII B(ii): Chest radiographic features of the patients studied.

	PPH	TPH	P
Number	38	16	NS
Enlarged proximal pulmonary arteries	89%	81%	NS
Cardiomegaly	82%	69%	NS
Attenuation of peripheral vessels	60%	56%	NS
Pleural effusion	3%	13%	NS
Venous congestion	0%	13%	NS
Lymphatic distension	0%	0%	NS

The most frequently noted abnormality was enlargement of the proximal pulmonary arteries. This was noted in 89% of our patients. Cardiomegaly, frequently with features characteristic of right ventricular enlargement, occurred in 82%. In 60% of patients peripheral vascular markings were attenuated. There was no evidence of venous congestion or lymphatic distension. Previous studies noted a slightly higher frequency(90-100%) of enlargement of the proximal pulmonary arteries but were otherwise similar[23,113,123]. The TPH group had essentially similar chest radiographic features. Anderson and his coworkers observed that in primary pulmonary hypertension the pulmonary artery is usually considerably enlarged, while in thromboembolic pulmonary hypertension it was more often normal or only slightly enlarged. Although our findings were different we were limited by not being able to trace some chest films for

personal review and therefore having to rely on the formal report issued by the radiologist at the time. We therefore could not ensure uniformity of diagnostic criteria.

VIII B(iii): Electrocardiographic features:

Table VIII B(iii): Electrocardiographic features of the patients studied:

	PPH	TPH	P
Number	37	16	
Sinus Rhythm	97%	94%	
Right ventricular hypertrophy	73%	38%	<Ø.Ø5
Right ventricular strain	65%	5Ø%	
Right axis deviation	94%	69%	<Ø.Ø5
Right atrial enlargement	39%	25%	
Pseudo left atrial enlargement	Ø%	6%	
Right bundle branch block	28%	25%	
Normal	Ø%	6%	

The abnormality most frequently noted in the PPH group was right axis deviation which occurred in 94%. The frequency of occurrence of right ventricular hypertrophy (73%) and right atrial enlargement (39%) was lower than that noted in previous studies[23,48,113,123]. In comparison with those reports our patients had a higher incidence of right bundle branch block. All but one of our patients were in sinus rhythm. A significantly lower frequency of right axis deviation ($p < Ø.Ø5$) and right ventricular hypertrophy ($p < Ø.Ø5$) was noted in the TPH group. This is in agreement

with previous observations of a lower prevalence of these two features in patients with chronic thromboembolic pulmonary hypertension[3,23].

VIII B(iv): Pulmonary function tests, arterial blood gas and haematocrit measurements.

Table VIII B(iv): Pulmonary function tests, arterial blood gas and haematocrit measurements in the patients studied (mean ± SD)

	PPH	TPH	P
	n = 19	n = 6	
FVC (% predicted)	81%±17%	91%±16%	
FEV_1/FVC	80%±12%	73%±9%	
TLC (% predicted)	84%±15%	107%±9%	<0.05
RV/TLC	34%±8%	38%±5%	
$TLCO_{SB}$	52%±16%	72%±33%	
KCO (% predicted)	67%±27%	90%±21%	
PO_2 (kPa)	10.6±2.0	10.3±2.1	
PCO_2 (kPa)	4.1±0.9	4.3±0.8	
Haematocrit	0.44±0.10	0.45±0.06	

FVC = forced vital capacity; FEV_1/FVC = ratio of forced expiratory volume in one second to forced vital capacity; TLC = total lung capacity; RV/TLC = ratio of residual volume to total lung capacity; $TLCO_{SB}$ = transfer factor for carbon monoxide (by the single breath method); KCO = transfer factor for carbon monoxide per litre of alveolar volume.

Williams and his colleagues asserted that lung volumes are generally normal in patients with pulmonary hypertension secondary to pulmonary vascular disease and that restrictive changes are more likely due to interstitial lung disease[129]. This opinion was challenged by the findings of Horn et al that a significant proportion of their patients with both primary and thromboembolic pulmonary hypertension demonstrated restrictive ventilatory patterns[47]. Their study relied only on radiographic and clinical exclusion of interstitial lung disease. This is unfortunate as Epler and his colleagues demonstrated that almost 10% of their patients with histologically confirmed diffuse infiltrative lung diseases had normal chest radiographs.[33] Nevertheless, that restrictive changes can occur in primary pulmonary hypertension without histological evidence of interstitial fibrosis was shown by the case reported by Scharf et al[107]. Burke et al noted a mean total lung capacity of 82.2% of predicted in 18 patients with primary pulmonary hypertension[9].

In order to ensure that no patient with pulmonary hypertension caused or aggravated by interstitial or obstructive lung disease influenced the results of this study, all those whose total lung capacity (TLC), forced vital capacity (FVC) or forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) was less than $^2/3$ the predicted value were excluded. Some patients with restrictive changes due to pulmonary vascular disease

alone may have been excluded on this basis. However, as lung histology was not available in the majority of these cases, this was the only means of selecting a group of patients whose clinical course was uninfluenced by the coexistence of interstitial lung disease. Despite this our findings show a small but significant restriction of lung volumes in the PPH group when compared with the TPH group (which had volumes close to predicted values). The mean transfer factor for carbon monoxide ($TLCO_{SB}$) was below predicted in both groups. The mean value of 52% predicted in the PPH group was similar to the results of both Williams et al[129]. and Horn et al[47] but less than the value of 71.8% predicted noted by Burke et al[9]. The mean $TLCO_{SB}$ in our TPH group was intermediate between the values found in previous studies[23,47,129]. Arterial PO_2 and PCO_2 values were similar to those noted in previous studies of PPH patients[47,129]. Benotti noted a slightly lower mean $PaCO_2$ in his patients with chronic thromboembolic pulmonary hypertension[3]. Mean haematocrit values were within the normal range in both groups.

VIII B(v): Radionuclide lung scans:

Table VIII B(v): Radionuclide lung scan data in the patients studied:

	PPH	TPH
Total number of patients	38	16
Number (% of total) patients who had scans	11(29%)	8(50%)
Type of Scan: Ventilation + perfusion	4	6
Perfusion only	7	2
Results: Normal	7	Ø
Low probability	4	Ø
High probability	Ø	8
Corroborative data:		
Angiogram + catheterization + histology	Ø	3
Angiogram + catheterization	7	4
Catheterization	2*	Ø
Histology	2	1

* One had SLE, the other the CREST variant of scleroderma.

No history of thromboembolism.

The successful use of pulmonary artery embolectomy in selected patients with chronic large vessel thromboembolic pulmonary hypertension[3,23,74,75,115], and of vasodilator therapy in some patients with PPH has made accurate diagnosis of the two conditions essential. The increased risks associated with pulmonary artery catheterization and open lung biopsy in this group of patients[39,114] have prompted the investigation of non-invasive means of identifying these conditions. Lung perfusion scanning using labelled macroaggregated human albumin provides an effective method of investigating the pulmonary circulation. Wilson et al[130] and Fishman et al[37] have shown that segmental or larger

defects occur in TPH whereas PPH patients either have a normal scan or show multiple bilateral subsegmental "patchy" areas of decreased perfusion. Wilson et al observed filling defects in the capillary blush between the arterial and venous phases of the pulmonary angiograms corresponding to these patchy areas and ascribed them to either primary pulmonary hypertension with secondary in situ thrombosis, small vessel thromboembolism, a combination of the two or a new as yet unidentified pathological entity. On the basis of a subsequent study Fishman et al classified patients with such patchy scans clearly in the category of primary pulmonary hypertension[37]. Nihill and McNamara noted similar filling defects in the capillary blush during angiography in patients with congenital left to right shunts and identified them as being indicative of elevation of pulmonary vascular resistance[78]. It is possible that they merely reflect a more severe degree of occlusive change in the small pulmonary vasculature.

Similar lung scan findings have been noted in PPH by D'Alonzo et al[23]. Our findings confirm these reports. All of the TPH patients who were studied had scans indicating a high probability of pulmonary embolism. Of the 11 patients studied in the PPH group, 4 had features indicative of a low probability of pulmonary embolism only while the other 7 had normal scans. No ventilation defects were noted in any of the 10 patients who had ventilation and perfusion scans.

The nature of the underlying condition was identified histologically or by pulmonary angiography in 17 of the 19 patients who were scanned. The two other patients had catheter proven pulmonary hypertension in the setting of a connective tissue disease (SLE and the CREST variant of scleroderma) with no evidence of interstitial lung disease clinically, radiographically or on pulmonary function testing and with no history suggestive of preceding episodes of thromboembolism. They were thus assumed to have primary pulmonary hypertension.

Although four fatalities have been reported in patients with obliterative pulmonary hypertension after perfusion lung scanning[16,130], no adverse effects were noted in our patients. A similar absence of complications has been noted by other authors[23,37,130]. Perfusion lung scanning has proved to be a safe and effective means of distinguishing primary pulmonary hypertension from chronic large vessel thromboembolic pulmonary hypertension.

VIII B(vi): Pulmonary angiography and lower limb venography:

Table VIII B(vi): Pulmonary angiograms and lower limb venograms in the patients studied:

	PPH	TPH	P
Number of patients studied (% of group)	22(58%)	15(94%)	
Pulmonary angiograms:			
Dilation of proximal pulmonary arteries	67%	80%	
Filling defects in main or lobar pulmonary arteries	0%	100%	<0.001
Small vessel occlusion	80%	47%	<0.05
Normal	10%	0%	
Lower limb venograms:			
Evidence of deep venous thrombosis	0%	57%	<0.01

None of the 22 PPH patients in whom pulmonary angiography was performed showed evidence of filling defects in the main or lobar pulmonary arteries. Generalised peripheral small vessel pruning was noted in 80%. Two-thirds showed dilatation of the main and proximal lobar pulmonary arteries. Pulmonary angiograms were normal in 10%. A slightly higher frequency of proximal artery dilatation was noted in the study by Fuster et al[39]. The angiographic features of their group were otherwise similar.

Occlusion of the main or proximal pulmonary arteries was demonstrated in all of the 15 TPH patients studied, but only 47% showed features of peripheral small vessel occlusion.

This was significantly lower than in the PPH group. Proximal dilatation occurred in 80%.

Microarteriographic techniques utilizing pulmonary wedge angiography have been suggested as a means of assessing the severity of the abnormal pulmonary haemodynamics[78], and of distinguishing PPH from small vessel thromboembolic pulmonary hypertension[992,117]. Pulmonary arteriographic studies on autopsy specimens suggested that PPH caused selective loss of arteriolar segments 100u to 280u in diameter whereas small vessel thromboembolic hypertension involved arterioles of less than 60u diameter[92]. This has been challenged by clinical studies that have shown occlusion of vessels from 1.5 to 2 mm diameter in some cases of thromboembolism[117]. None of our patients was subjected to pulmonary wedge angiography.

Several reports have stressed the increased risks associated with cardiac catheterization and pulmonary angiography in these patients[26,114,126]. Of the 120 PPH patients subjected to catheterization by Fuster and his coworkers, 5 died as a result of the procedure.[39] Transient severe pulmonary hypertension following the injection of the radiographic contrast medium used in this procedure has been reported and probably occurs more frequently than is generally recognized as most centres do not measure pulmonary artery pressures continuously during pulmonary angiography[26,114,126]. The mechanism by which cardiac arrest is caused in this situation has not been fully

elucidated. It may be due to reflex pulmonary vasoconstriction following injection of the dye, sludging of red blood cells in small pulmonary vessels[26] or a cardiac arrhythmia initiated by transient coronary artery hypoxaemia as a bolus of contrast medium passes[114]. No adverse effects of cardiac catheterization or pulmonary angiography occurred in our patients.

Ascending lower limb venography was normal in all 5 PPH patients on whom it was performed. A significantly higher proportion (57%) of the 7 TPH patients who were studied showed evidence of deep venous thrombosis.

VIII B(vii): Haemodynamic data at diagnosis:

Table VIII B(vii)a: Haemodynamic data at diagnosis in the patients studied (mean ± SD)

	PPH	TPH	P
Number of patients studied (% of group)	32(84%)	14(88%)	
Mean pulmonary artery pressure (mmHg):	64.5±18.7	52.9±15.5	<0.05
Mean systemic blood pressure (mmHg):	95.2±14.2	105.5±17.2	
Mean right atrial pressure (mmHg)	8.9±5.6	11.2±6.2	
Pulmonary capillary wedge pressure (mmHg)	9.3±3.9	12.1±4.7	
Cardiac output (l/min)	4.2±1.4	4.3±1.1	
Cardiac index (l/min/m^2)	2.7±1.0	2.5±0.7	
Stroke volume index (ml/beat/m^2)	36±15	35±20	
Pulmonary vascular resistance (units)	15.2±9.3	9.7±2.9	
Systemic vascular resistance (units)	22.8±7.8	24.1±7.6	
Arterial oxygen saturation (%)	94.4±2.6	88.1±4.8	<0.01

Mean pulmonary artery pressure was significantly greater in the PPH group. A similar trend noted by D'Alonzo et al did not attain statistical significance[23].

The greater ventilation/perfusion mismatching produced by pulmonary thromboembolism is reflected in the significantly lower arterial oxygen saturation in this group.

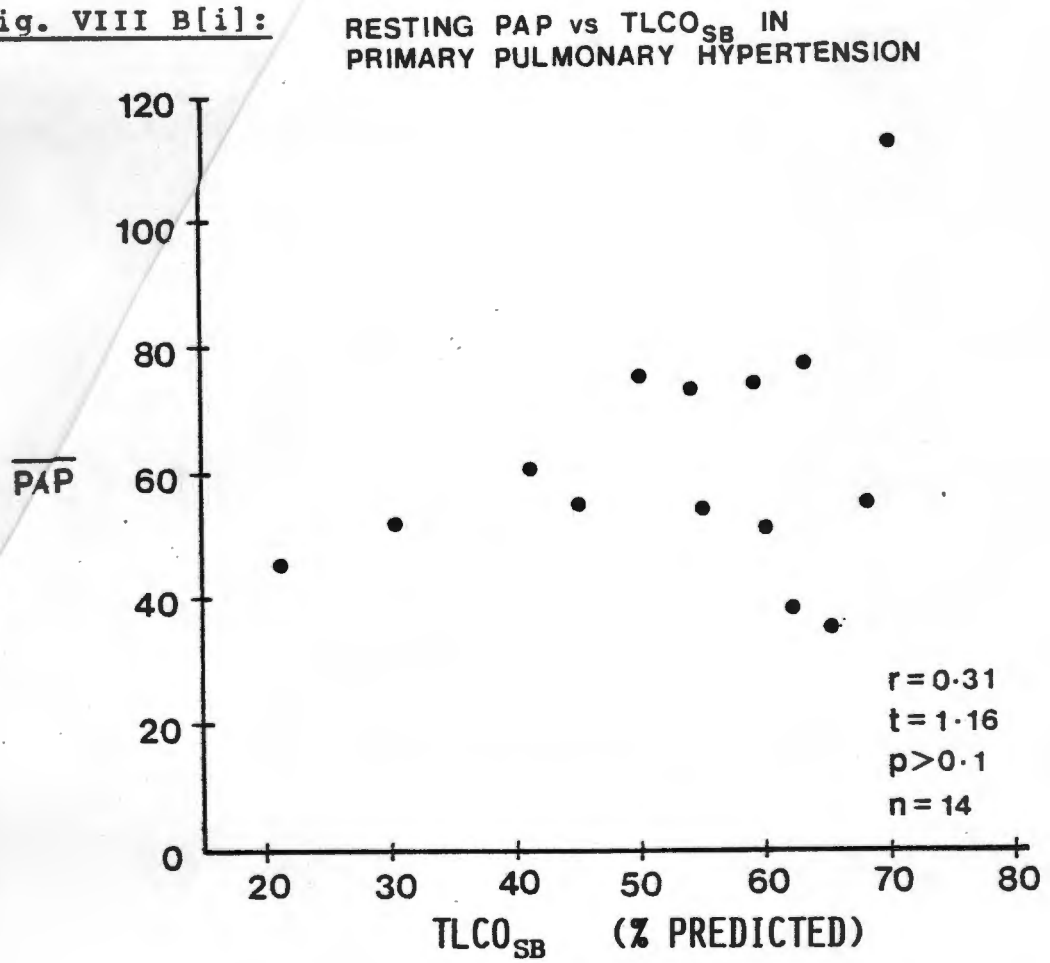
The haemodynamic findings in the PPH patients studied by Hughes and Rubin[48] and Fuster et al[39] as compared with the findings of the present study are outlined in Table VIII B(vii)b.

Table VIII B(vii)b: Haemodynamic data of PPH patients compared with previous studies (mean ±SD)

	Present study	Hughes & Rubin	Fuster et al
Mean pulmonary artery pressure (mmHg)	64.5±18.7	57.8±13.6	64
Cardiac output (l/min)	4.2±1.4	4.0±1.8	
Cardiac index (l/min/m_2)	2.7±1.0		2.2
Pulmonary vascular resistance (units)	15.2±9.3	14.5±7.3	
Arterial oxygen saturation (%)	94.4±2.6		91

Benotti and his colleagues found a fair correlation ($r = \emptyset.65$) between the severity of the pulmonary hypertension and the severity of arterial hypoxaemia in 15 patients with TPH[3]. We found no correlation between the resting mean pulmonary artery pressure and the transfer factor for carbon monoxide in our group of patients. (Fig. VIII B[i])

Fig. VIII B[i]:



VIII C: Exercise Studies:

Four patients were subjected to a stage 1 exercise study at the time of diagnosis. They achieved a mean maximal power output of 56% predicted with a range of 43 to 74%. The mean arterial desaturation on exercise was 3.3% with a range of Ø to 9%. All showed an excessive heart rate response which approached the predicted maximum heart rate. A sub-normal blood pressure response occurred in two patients. Three patients showed mild hyperventilaton and tachypnoea throughout the test. In the case of the 4th patient, ventilation was initially normal but later rapidly increased to approach the predicted maximum. Exercise was stopped because of leg fatigue in two patients and dyspnoea in the others. A 5th patient whose initial exercise test was abandoned as she became hypotensive within three minutes of commencing exercise was again tested 3 years after diagnosis and provided additional data which was included in the assessment of the correlation of resting $P_{ET}CO_2$ with percentage predicted power output attained (Fig. VIII C[iii]). No correlation was noted between the percentage predicted maximum power output achieved and the resting mean pulmonary artery pressure, right atrial pressure or stroke volume index. There was no correlation between the percentage desaturation on exercise and the resting mean pulmonary artery pressure (Fig. VIII C[i]).

Fig. VIII C[i] A: Resting mean pulmonary artery pressure (PAP), B: Mean right atrial pressure (RAP), and C: Stroke volume index plotted against % predicted maximal power output attained in the 4 patients tested. Mean RAP was not recorded in one patient. D. Resting mean pulmonary artery pressure plotted against % desaturation on exercise. No significant correlation was noted.

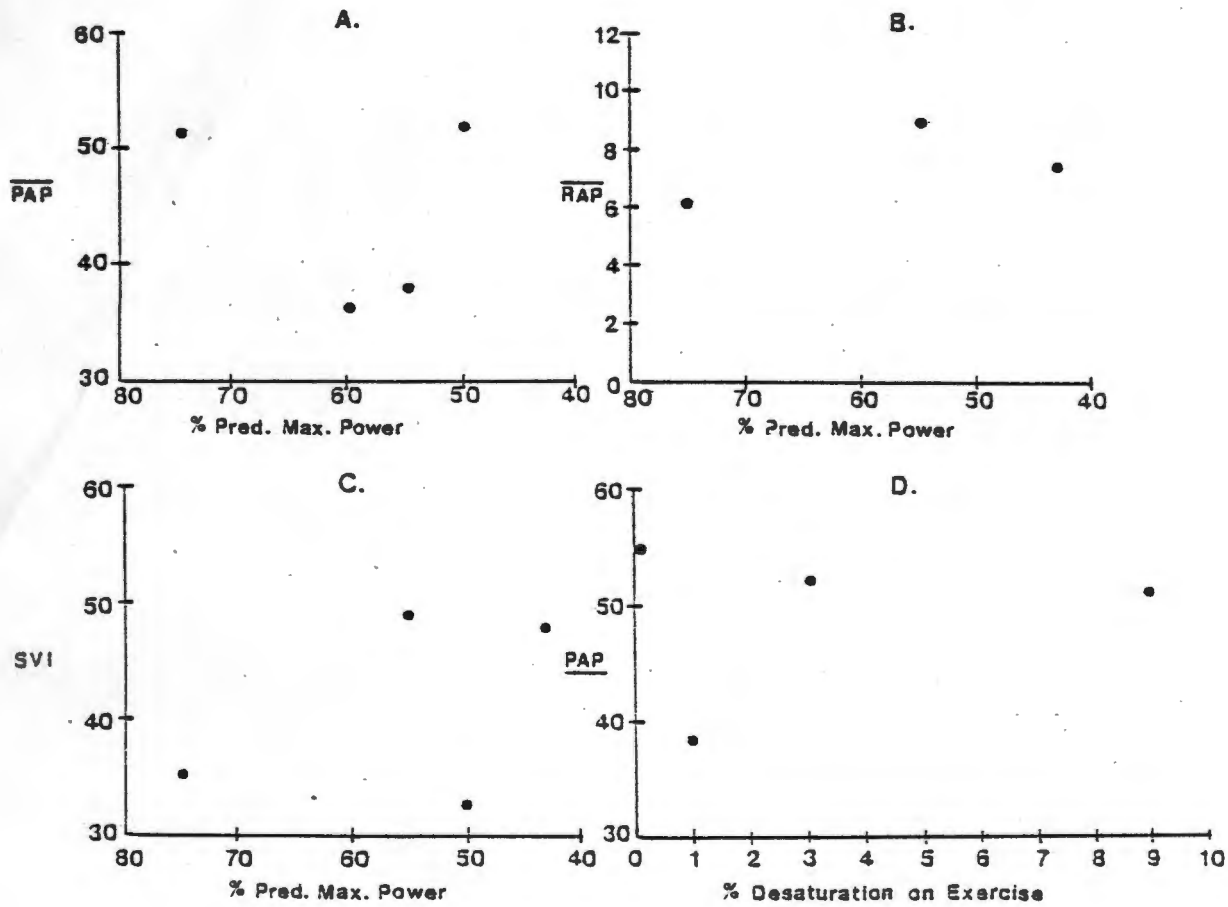


Fig. VIII C[ii]: End tidal PCO_2 during exercise vs stage of exercise as reflected by % predicted maximum power output as measured in patients 2, 6, 8 and 32. End tidal PCO_2 is low at rest and at various stages of exercise.

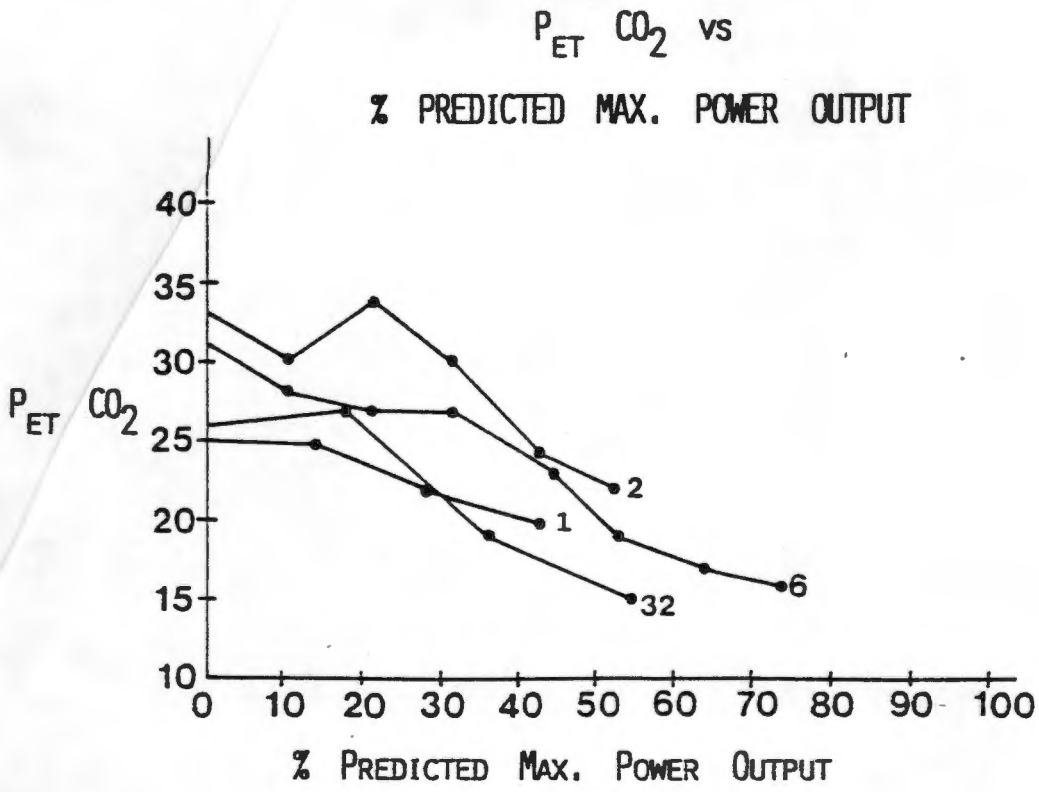
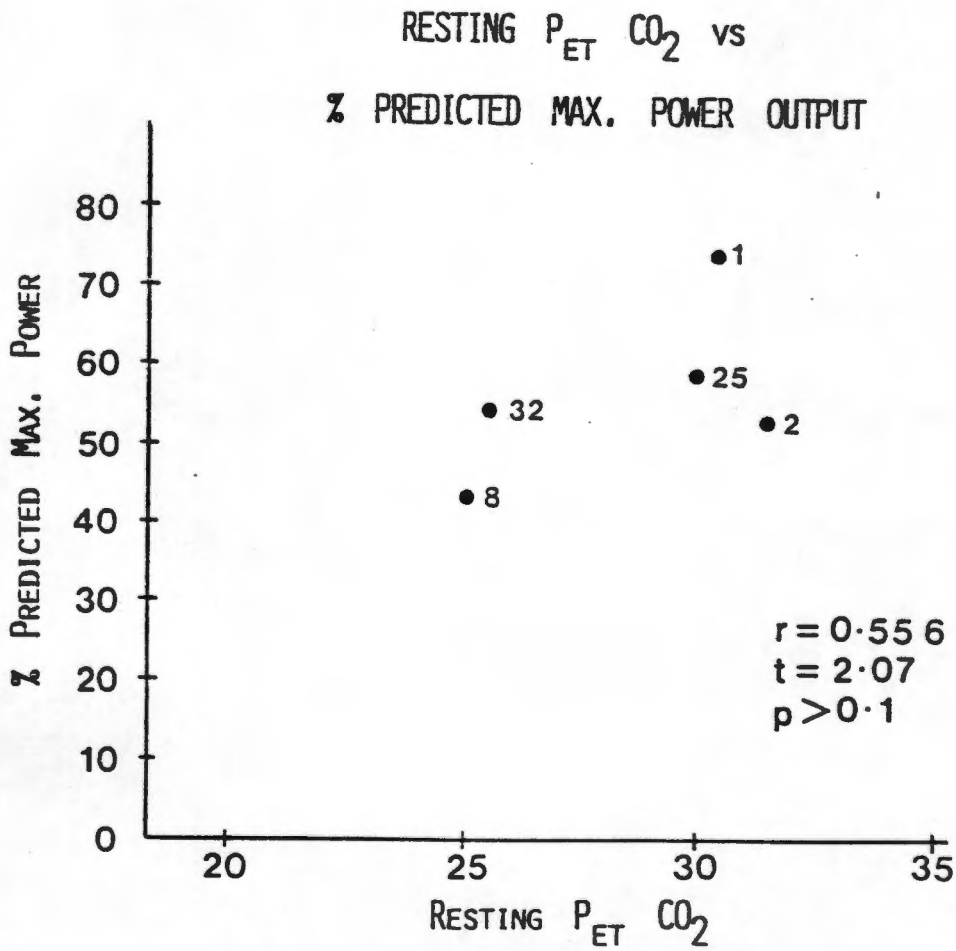


Fig VIII C[iii]: Resting end tidal PCO_2 vs % predicted maximum power output as measured in patients 1, 2, 8, 25 and 32. No correlation was noted.



During exercise the $P_{ET}CO_2$ was depressed earlier and to a greater degree than in normal subjects in whom the P_{ET} CO_2 would show little or no change at comparable levels of exercise[53] (Fig. VIII C[ii]). This is probably due to an increase in physiological dead space caused by pulmonary vascular disease.

Moreover there was no correlation between the resting $P_{ET}CO_2$ and the percentage predicted maximal power output attained (Fig VIII C[iii]).

We were thus unable to show any correlation between the parameters measured during stage 1 exercise studies and the severity of the pulmonary hypertension at diagnosis in these patients.

Stage 1 exercise studies were repeated in 3 patients. A patient with CREST variant of scleroderma who had noted progressive worsening of dyspnoea on effort showed a 60% reduction of maximal power output and a more severe tachycardia during exercise compared with a test done 3 years earlier. The second patient had PPH associated with previous chronic active hepatitis. Her effort tolerance had remained good and a repeat exercise study showed that only a slight reduction in maximal power output had occurred during the $3^1/2$ years since the previous study. The last patient had PPH associated with SLE. She described a mild improvement in her effort tolerance. Her maximal power output was moderately improved. It would therefore appear that the

patients' subjective assessment of exercise tolerance reflected measured exercise capacity with a fair degree of accuracy. As repeat catheterizations were not performed on these patients we were unable to assess whether changes in maximal power output parallelled changes in pulmonary vascular involvement as has been suggested by Janicki et al[52].

VIII D: Response to vasodilator therapy.

The observation that medial hypertrophy of the muscular arteries and muscularization of the arterioles is the initial structural abnormality in PPH has led to the postulate that the primary defect is probably prolonged vasoconstriction [31,122,132]. This has prompted the use of vasodilator agents in an attempt to reverse the vasoconstriction before irreversible changes develop. Dresdale described the use of vasodilators in his early paper on this subject[29]. More recently, a number of papers have described beneficial effects from the use of vasodilators[12,66,67,86,101,125].

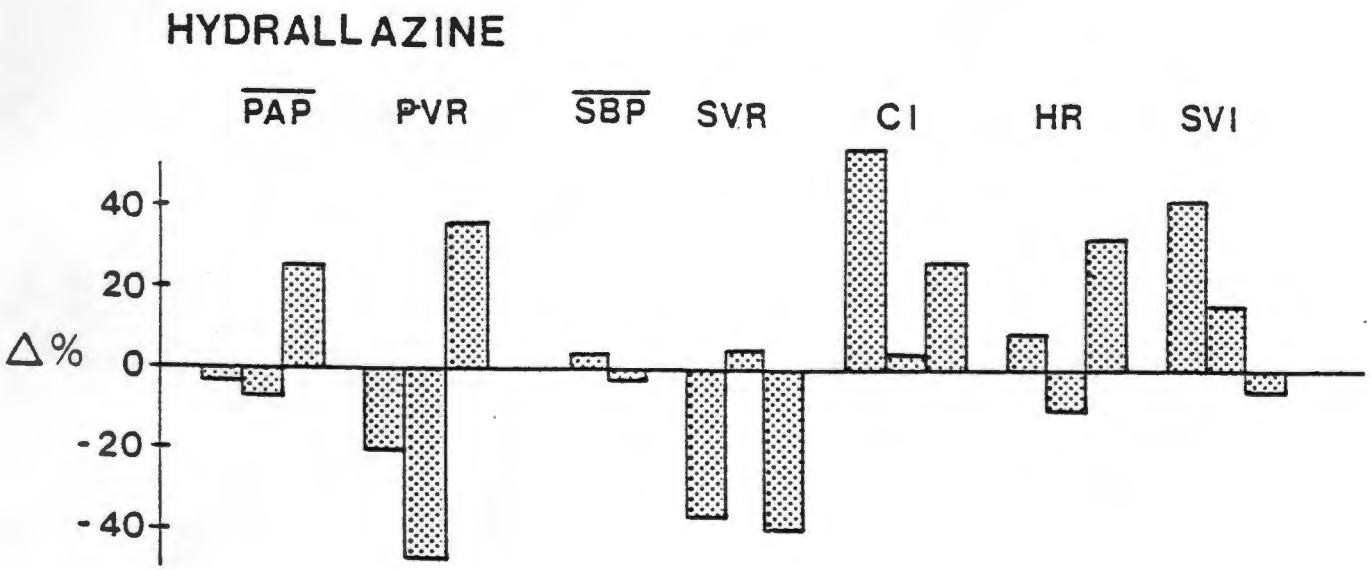
We evaluated the effects of 10 vasodilator agents in 13 patients. Not all patients were treated with the same agents as treatment policy was modified during the study period.

Table VIII D(i): Vasodilator agents evaluated:

Patient:	1	2	8	9	13	16	21	22	23	25	30	31	32
Hydrallazine	+	+	+										
Isosorbide						-							
Dinitrate	+	+	+										+
Isoprenaline	+	+								+		+	
Nifedipine	+	+	+										+
Amyl Nitrate				+			+	+	+				
Phenylephrine				+				+	+				
Diazoxide	+				+	+					+	+	
Acetylcholine							+						
Labetolol												+	
Prazosin													+

VIII D(i): Hydrallazine:

Fig. VIII D(i): Acute effect of hydrallazine in the 3 patients tested:



Hydrallazine (50mg by mouth) was given to 3 patients. Two had a significant (greater than 10%) reduction in pulmonary vascular resistance (PVR) while a significant rise occurred in the third. None of the patients showed a significant reduction in mean pulmonary artery pressure (PAP). One showed a 25% elevation. Mean systemic blood pressure (SBP)

remained relatively constant: a significant reduction of systemic vascular resistance (SVR) in two patients was compensated by a significant elevation in cardiac index (CI) which was achieved by a compensatory tachycardia in one and an increase in stroke volume index (SVI) in the other. In the third patient the CI remained stable as a significant increase in stroke volume index was compensated by significant reduction in heart rate.

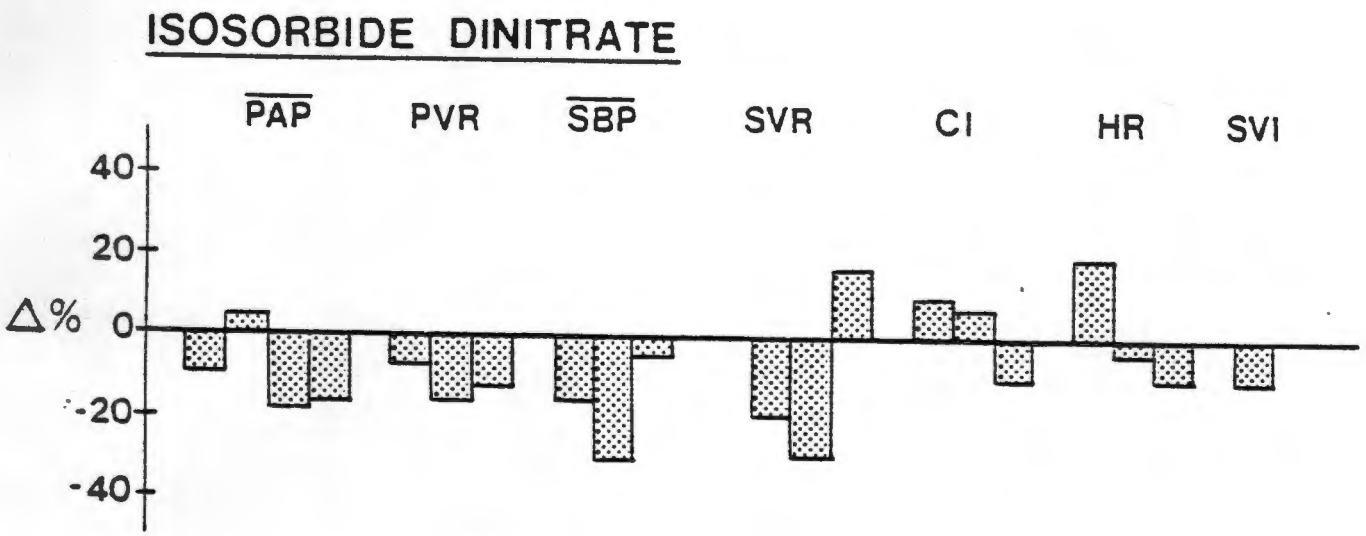
Rubin and Peter noted a reduction of PVR with a concomitant increase in cardiac output (CO) both at rest and on exercise in 4 patients treated with this agent. There was no change in mean pulmonary artery pressure. These effects persisted after follow up for 3 to 6 months[102]. Lupi-Herrera et al identified a subgroup of their patients with PAP <60 mmHg, PVR <15 units/m^2 and PVR/SVR ratio <0.7 who showed a similar response to hydrallazine while the remainder (who had a higher PAP and PVR) showed a significant reduction in SVR only[67].

Adverse effects of hydrallazine have been frequently reported. Kronzon et al reported a rise of PAP in 2 patients due to an increase in cardiac output in the face of an unchanged pulmonary vascular resistance.[60] Four of the patients studied by Packer and his colleagues became symptomatically hypotensive within 24 hours of the initiation of therapy. One of these patients died[85]. Severe hypotension occurred in one of the patients studied by Hermiller et al[44].

There would thus appear to be a group of patients with a responsive pulmonary vasculature who benefit from hydrallazine therapy. However, the use of this agent in patients with a fixed pulmonary vascular resistance may be hazardous. Direct haemodynamic monitoring is essential in all patients during a trial of therapy.

VIII D(ii): Isosorbide dinitrate:

Fig VIII D(ii): Acute effect of isosorbide dinitrate in the 4 patients studied:

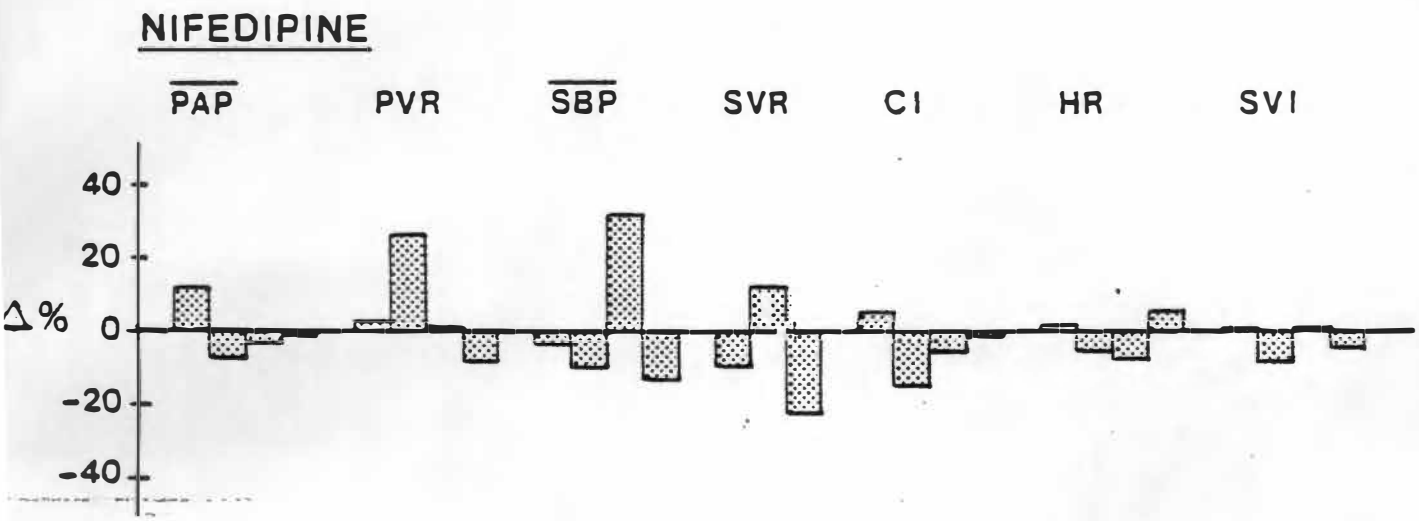


Isosorbide dinitrate 10 mg orally was given to 4 patients. Two showed a significant reduction in PAP. Although the PAP in the third patient was unchanged, the PVR was significantly reduced. Two patients had significant reductions of SBP and SVR. The effect on heart rate, CI and SVI was inconsistent.

Our findings are in accord with those of Hermiller and his colleagues[44] who showed that isosorbide dinitrate was the only one of 6 vasodilators tested to achieve a significant reduction of both PAP and PVR. Pearl and his coworkers found a similar significant reduction in both PAP and PVR in 9 patients with pulmonary hypertension. Five of their 6 patients on long term therapy experienced an improvement in their symptoms. Isosorbide dinitrate, unlike other vasodilators, produces systemic venodilatation and probably pulmonary arterial dilatation at a dose that produces only minimal systemic arterial dilatation[86]. This may account for the relative freedom from the systemic hypotension which has limited the use of other vasodilators.

VIII D(iii): Nifedipine:

Fig. VIII D(iii): Acute effect of nifedipine in the 4 patients studied:



No significant reduction in PAP or PVR occurred in the 4 patients treated with 20 mg of nifedipine sublingually. A significant elevation of PAP occurred in 1 patient due to a mild increase in both PVR and CI while another patient showed a significant increase in PVR associated with a significant decrease in cardiac index. Systemic blood pressure was significantly reduced in 2 patients.

Camerini and his coworkers were the first to report a pronounced fall in PVR and SVR with a rise in CO after sublingual nifedipine in a patient with severe PPH. This was accompanied by a marked improvement in symptoms and was maintained over the 3 month follow up period[12]. Beneficial acute and long term haemodynamic changes associated with improvement in symptoms were achieved by this agent in a patient with late stage PPH studied by De Feyter and his colleagues[26]. Similar haemodynamic changes after nifedipine were noted by Rubin et al in their 9 patients.[101] Heart rate and PAP did not change but equilibrium gated blood pool radionuclide imaging demonstrated a reduction in right ventricular end-diastolic and end-systolic volumes with an increased right ventricular ejection fraction indicative of improved right ventricular performance associated with the reduction in PVR. These effects persisted after follow up periods ranging from 4 to 14 months. Other authors have also reported the beneficial haemodynamic effects of nifedipine therapy[81,131].

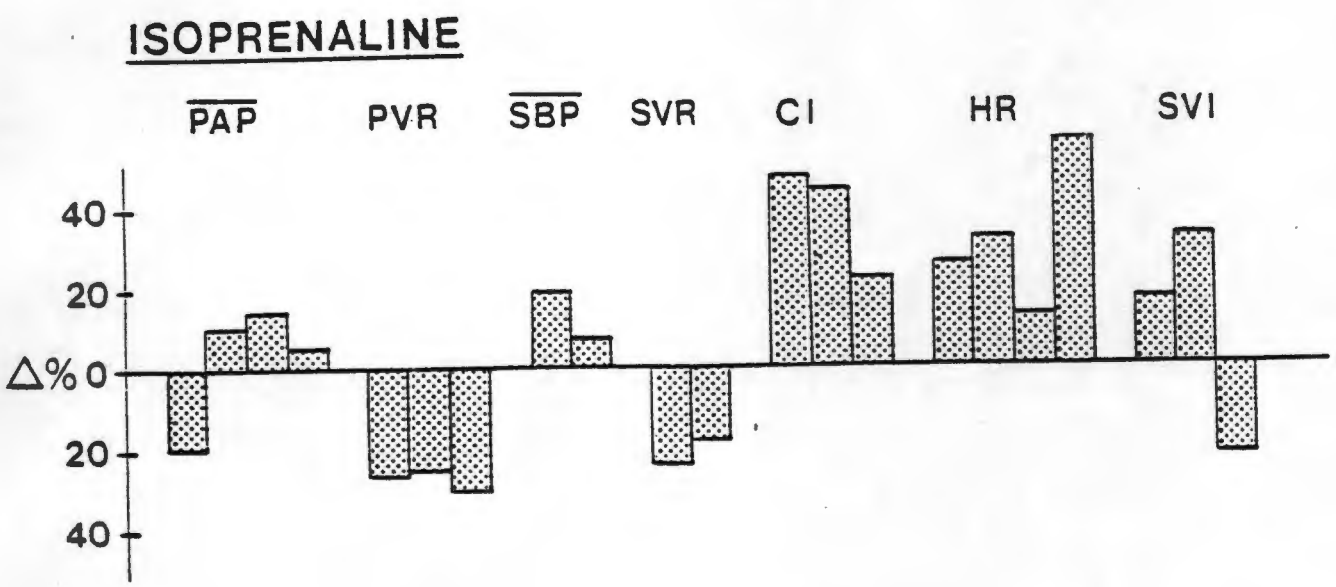
However, not all reports have been as encouraging. Dalal and his colleagues reported the onset of azotaemia and right ventricular failure in a 23 year old woman when the nifedipine dose was doubled after an initially encouraging response to 10 mg three times daily. She died a day later. The authors postulated that the negative inotropic effect of the nifedipine may have played a part in her deterioration[22]. Berkenboom found no haemodynamic improvement after nifedipine administration to a 36 year old

woman with PPH[4]. Our findings were in agreement with those that failed to show any beneficial effect of nifedipine therapy.

Other calcium antagonists have been evaluated in the management of this condition. Kambara and his colleagues showed that diltiazem effected a significant reduction in PAP and PVR and a significant increase in CI when given intravenously and, subsequently, orally over eleven months[54]. Landmark et al noted that intravenous verapamil caused a slight reduction in PAP but that in some patients it exerted a marked negative inotropic effect with a concomitant increase in PVR[61].

VIII D(iv): Isoprenaline

Fig. VIII D(iv): Acute effects of isoprenaline in the 4 patients tested:



Four patients were treated with isoprenaline: two were treated with an intravenous infusion while the others received 15 mg sublingually. In all three patients in whom these parameters were measured, PVR and SVR showed significant reductions while the cardiac index and heart rate increased significantly. Only one patient showed a significant reduction in PAP. In two patients the PAP increased significantly as the reduction in PVR was insufficient to compensate for the increase in CI produced by isoprenaline. The PAP remained constant in the fourth patient despite a significant reduction in PVR. An additional patient who was given intravenous isoprenaline developed a severe tachycardia which precipitated right ventricular failure. No haemodynamic readings were recorded.

Other authors have reported similar results. Lee and his colleagues observed a reduction of PVR and increase of CI after 20 mg sublingual isoprenaline in 14 patients[63]. Hermiller et al reported a reduction in PVR, SVR and SBP with an increase in cardiac index in their patients[44]. Daoud et al showed a reduction in PVR in 5 of their 6 patients[24]. Shettigar and his coworkers' report of an initially favourable response but subsequent progression of the disease despite continued therapy[111] brought the efficacy of maintenance therapy into question. However both Pantano[85] and Pietro et al[88] have subsequently reported persistent haemodynamic and symptomatic benefit from long term administration of sublingual isoprenaline. The study by Lupi - Herrera et al purported to shed some light on the marked variability of the response to isoprenaline in different patients: only those patients with a moderately elevated PVR responded; those with severely elevated PVR did not respond. The authors suggested that non-responders represented a more advanced stage of the disease process.[66] However, the study by Hermiller did not confirm these findings[44].

VIII C(v): Diazoxide:

Using the treatment protocol first suggested by Wang et al[125] we noted a significant reduction in PVR in 3 of the 4 patients who were treated with this agent. One of these showed a significant concomitant reduction of PAP with no change in SBP, SVR or CI while the other 2, in whom PAP remained unchanged, showed a significant reduction in SVR and SBP accompanied by a significant increase in CI. One patient developed severe hypotension with confusion and sinus arrest after intravenous injection of 300 mg of diazoxide.

Other authors have noted similar responses with a reduction in PVR, SVR and SBP accompanied by an increase in CO[58,125]. Hermiller et al noted in addition a rise in PAP due to an increase in cardiac output disproportionate to the reduction in PVR[44].

Serious side effects have been noted following administration of diazoxide. Of three patients to whom this agent was administered by Buch and Wennevold one developed asystole, one developed total atrioventicular block and the third developed severe systemic hypotension[8]. Rubino and Schroeder reported a patient who developed ventricular tachycardia and died shortly after injection of 300 mg of dizoxide[103]. Elkayam noted severe hypotension and supraventricular tachycardia following injection of a similar dose[32].

The high risk of serious side effects necessitates direct haemodynamic and electrocardiographic monitoring during intravenous administration of this agent.

VIII F(vi): Prazosin

While other authors have found this effective in reducing PVR and PAP and increasing CO[32], we noted no significant effect after giving Ø.5 mg orally to a single patient.

VIII D(vii): Other agents:

Amyl nitrate, acetylcholine and labetolol had no significant effect on PAP and PVR. Acetylcholine has been noted previously to produce an inconsistent response with no effect on the resting cardiac output[90,106]. Amyl nitrate and labetolol caused a marked reduction SBP and SVR while phenylephrine caused a significant rise in PAP and PVR in the 2 patients to whom it was administered.

Two further newly developed vasodilating agents, prostacycline and captopril, were not used in our study. Prostacycline has been shown to reduce PVR, PAP and SBP as well as preventing platelet aggregation within the pulmonary vascular bed[116]. A continuous infusion over 13 months has been effective in treating a woman with PPH[45]. Other investigators have found it a useful agent in assessing the

responsiveness of the pulmonary vascular bed[112]. The ability to titrate the dose against the haemodynamic effect, the potency of this agent as a pulmonary vasodilator and the ability to reverse rapidly any adverse haemodynamic effects by discontinuing the infusion suggest that it is particularly suitable for the initial testing of a patient's responsiveness to vasodilators. Severe side effects of nausea, headache and cutaneous flushing prevent its utlization in a number of patients[100].

The serum angiotensin-converting enzyme inhibitor, captopril, was initially reported to relieve symptoms and improve right ventricular performance in patients with PPH[49]. Other authors have subsequently shown no significant effect on the pulmonary vasculature in the majority of their patients treated with this agent[64,94].

Unlike other authors we were unable to identify a group of patients who consistently responded to the various agents tested in our study. Different agents showed different degrees of effectiveness in different patients. While isoprenaline, diazoxide and isosorbide dinitrate were reasonably effective in reducing PVR, their effect on pulmonary artery pressure was less consistent.

VIII D(viii): Future possibilities:

Vasodilator therapy may be effective in a larger proportion of PPH patients if they are diagnosed before irreversible changes develop in the pulmonary arterioles. Non-invasive measurement of pulmonary artery pressure by doppler promises to be a valuable means of detecting and monitoring progression of pulmonary hypertension[21].

Effective pharmacological reduction of pulmonary artery pressure is limited by the severe systemic effects produced by vasodilator agents currently available. The development of an agent acting selectively on the pulmonary vasculature and which could be administered orally would be a great advance.

VIII E: Clinical course:

VIII E(i): Primary and chronic large vessel thromboembolic pulmonary hypertension:

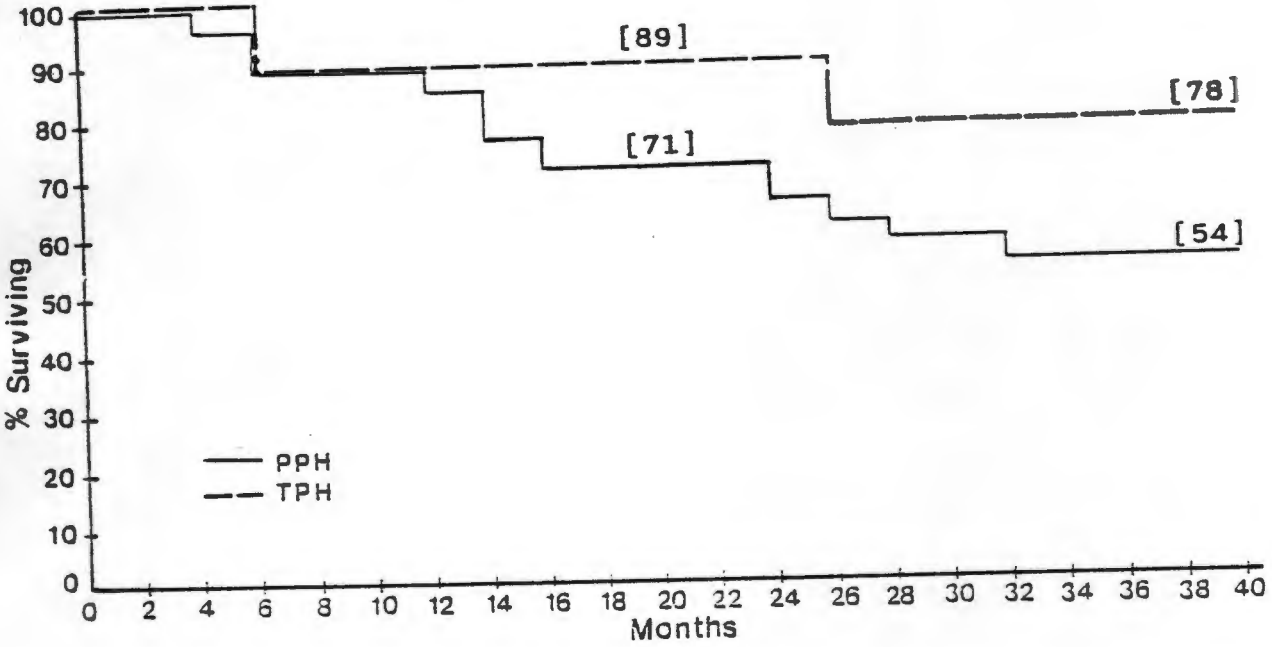
Adequate follow up information to 40 months was available on 28 patients in the PPH group and 9 patients in the TPH group. The characteristics and survival curves of the two groups were analyzed separately and are outlined in Table VIII E[i] and Fig. VIII E[i] respectively. There was no significant difference between the clinical and haemodynamic features of the 2 groups.

Table VIII E[i]: Comparative features of PPH and TPH patients followed 40 months or more from onset.

	PPH	TPH	P
Number	28	9	
Age at presentation (years)	32.0	41.6	NSS
No. (%) who had catheterization	24(86%)	6(67%)	NSS
PAP (mmHg)	67.7	57.8	NSS

NSS = Not statistically significant.

Fig. VIII E[i]: Survival to 40 months of patients with PPH and TPH.



Fifty-four per cent of the PPH group survived 40 months from the onset of symptoms. The significance of this finding is weakened by the fact that, because of inadequate information, 10 patients could not be included in the analysis of survival. This could be construed as showing that all 10 had died without our being informed. Although this may be true of two patients who had severe pulmonary hypertension it does not necessarily apply to the remaining 8 all of whom had only moderate pulmonary hypertension. One is still attending our clinic 36 months after the onset of symptoms, is clinically stable and is highly likely to survive well beyond 40 months; three residents of neighbouring southern African countries were seen shortly before a period of intense socio-political upheaval in those countries and may have emigrated or moved as part of the immense changes those communities underwent. The doctors attending two of these cases wrote to

notify us of improvement of clinical and in one case electrocardiographic features one and two years after being seen respectively. Each of these 8 patients was living as part of a family who could have replied to our letter of enquiry had they still been resident at their original address.

Two of our patients showed improvement in symptoms and clinical features. Effort tolerance improved from NYHA grade 3 to grade 1, and right ventricular 3rd and 4th heart sounds disappeared over a follow up period of 10 years in the case of the first patient. The second patient (with SLE) showed a less dramatic improvement in effort tolerance with disappearance of right ventricular 4th sound and moderate improvement in measured maximal power output over a period of 3 years. Repeat cardiac catheterization has not been performed as the attending physician felt that the slight associated risk was not warranted in the first patient and the second patient is satisfied with her present condition. Two other patients, both on long term vasodilator therapy, appear to have stabilised. Their symptoms and physical signs have remained unchanged over 4 and 8 years follow up respectively. One of these patients, who has PPH associated with chronic active hepatitis, showed a slight reduction in measured maximal power output over the first 2 years of follow up (700 to 600 kpm/min) but showed no further deterioration when tested 2 years later. The second patient, who became hypotensive after 3 minutes of exercise at the

initial assessment, performed far better 8 years later achieving a maximal power output of 500 kpm/min (60% predicted maximum) with a normal blood pressure response. Although we have classified her as having remained stable on the basis of our clinical assessment, the improved exercise test result may reflect true improvement. Repeat catheterization has not been performed.

Walcott and his colleagues reported a 44% three year survival with only 3 of their 23 cases surviving for longer than 10 years.[123] Fuster et al reported a median survival from diagnosis to death of 1.9 years (range 0 to 16 years) in their 112 patients. More than three-quarters of the deaths in their study occurred within 5 years of diagnosis[39]. The condition was thus thought to have a rather dismal prognosis but this view has had to be revised in the light of a recent report by Rozkovec et al that 12 of their 34 patients survived longer than 5 years and that 4 patients showed evidence of regression of the disease[99].

Although a greater proportion of our TPH group than our PPH group survived 40 months, the difference was not statistically significant.

VIII E(ii): <u>PPH associated with connective tissue disease:</u>

Six of the PPH patients had an associated connective tissue disease: two had the CREST variant of systemic sclerosis, three had SLE and one had juvenile chronic arthritis. The

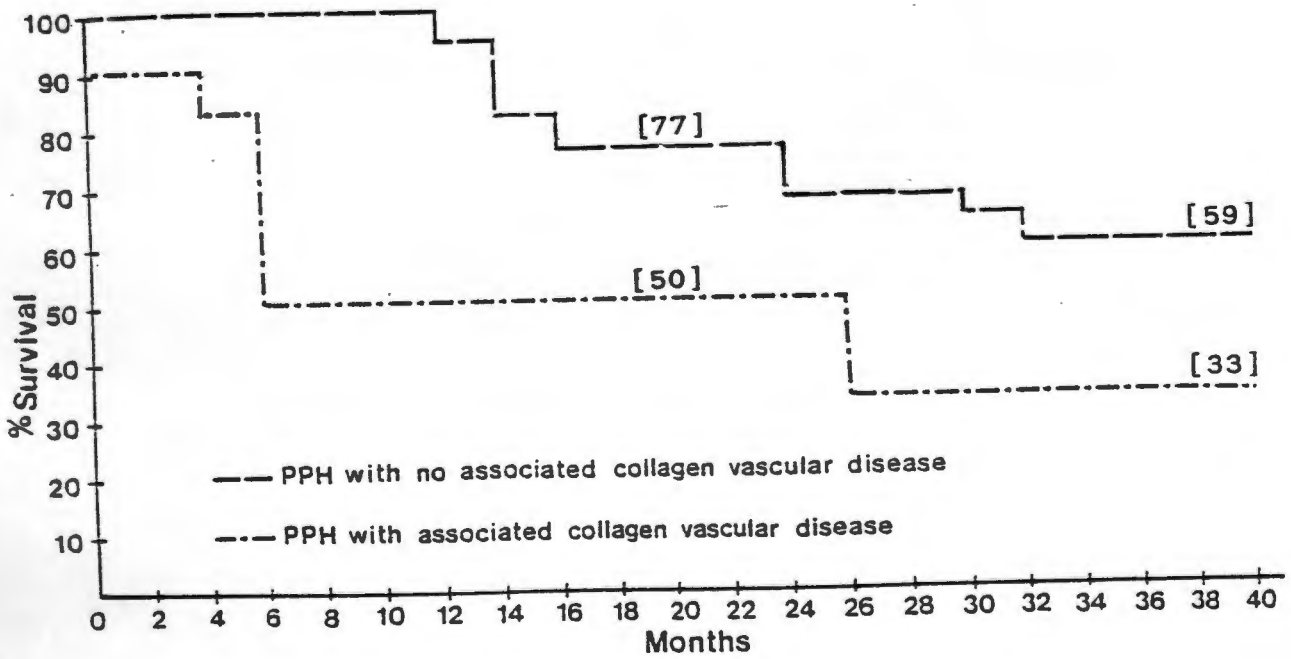
characteristics and survival curves of the PPH patients with and without an associated connective tissue disease were analysed separately and are outlined in Table VIII E[ii] and Figure VIII E[ii] respectively.

Table VIII E[ii]: Comparative features of PPH patients with and without an associated connective tissue disease:

	PPH without connective tissue disease	PPH with connective tissue disease	P
Number	22	6	
Age at presentation (years)	31.0	37.3	NSS
Number (%) who had catheterization	20(91%)	3(50%)	NSS
PAP (mmHg)	71.2	45.0	<0.05

NSS = Not statistically significant.

Fig VIII E[ii]: Survival to 40 months of PPH patients with and without associated connective tissue disease.



Despite significantly less severe pulmonary hypertension at the time of initial assessment, the group with an associated connective tissue disease had a lower 40 month survival. However, as the group was relatively small this difference did not reach statistical significance. A similar trend was noted by Rozkovec and his colleagues: the mean survival of their PPH patients with an associated connective tissue disease was 3.4 years while that of the whole group was 7.3 years. However, as the number of patients with associated connective tissue diseases in their series was also relatively low, this difference was not significant[99]. A study including a larger number of patients with PPH with an associated connective tissue disease is needed to show whether the prognosis of such patients is indeed worse than other PPH patients.

VIII E(iii): Effect of long term anticoagulant therapy on survival.

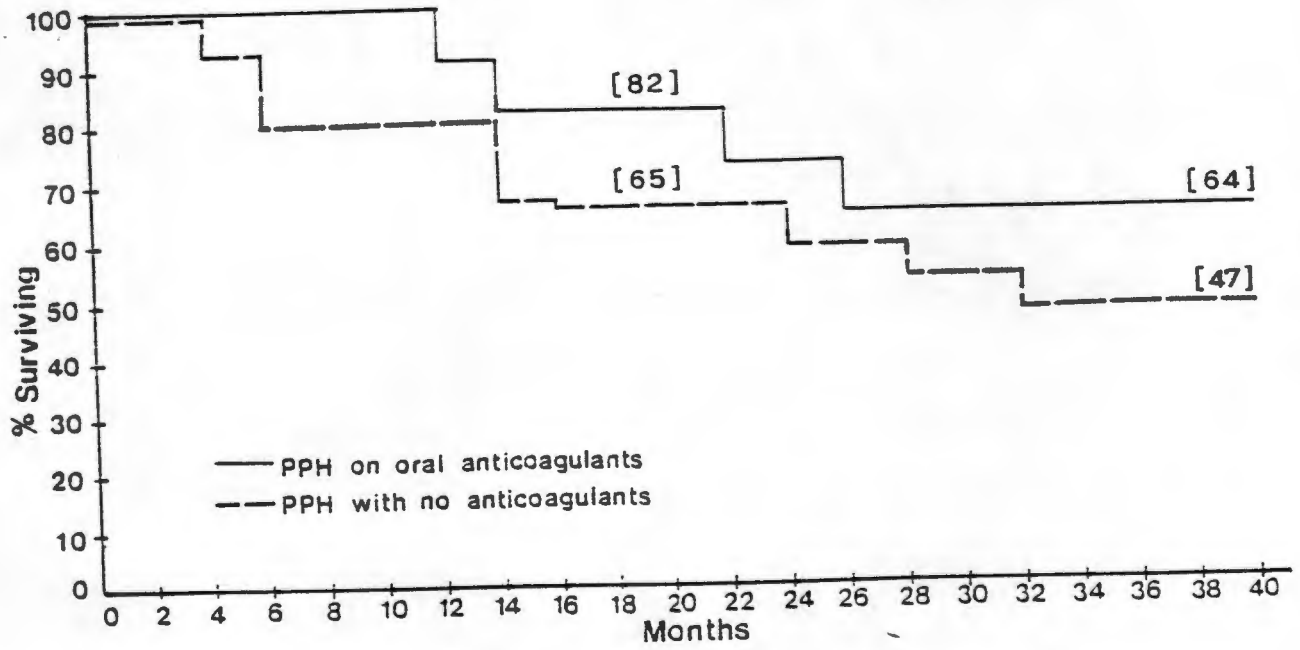
Eleven patients received long term anticoagulant therapy. There was no significant difference between the initial clinical and haemodynamic characteristics of the patients who were treated with chronic anticoagulation and those who were not (Table VIII E[iii]).

Table VIII E[iii]: Comparative features of patients who received long term oral anticoagulant therapy and those who did not.

	No anti-coagulants	Anti-coagulants	P
Number	15	11	
Age at presentation (years)	32.5	31.3	NSS
Number (%) who had catheterization	11(73%)	10(91%)	NSS
PAP (mmHg)	69.3	65.8	NSS

NSS = Not statistically significant.

Fig VIII E[iii]: Survival to 40 months of PPH patients with and without anticoagulant therapy.



The trend towards improved survival shown by the patients on anticoagulant therapy did not attain statistical significance. Fuster and his colleagues showed a small but significant improvement in survival of PPH patients on long term oral anticoagulants[39].

VIII E(iv): Long term vasodilator therapy.

Long term vasodilator therapy was attempted in 6 patients using agents to which the patient had responded favourably during testing. The treatment was withdrawn from 3 patients because of severe side effects. Isosorbide dinitrate, hydrallazine and nifedipine all caused severe headaches. In 1 patient the introduction of diazoxide was reputedly associated with the development of peripheral oedema and it was thus discontinued by the doctor attending her.

A fourth patient who died while still on sublingual isoprenaline underwent a repeat catheterization shortly before her death. This showed that the PAP had risen significantly since the original study three months previously (from 77 to 90 mmHg). Two patients are still on vasodilator therapy after 37 and 96 months respectively. The first patient (who is on isosorbide dinitrate) showed no significant change in PVR when recatheterized 13 months after the initial study. The second patient who is on isosorbide dinitrate, verapamil and a thiazide diuretic has not been recatheterized. A reversible deterioration of her effort tolerance corresponding with a period of withdrawal of her medication suggests that the therapy is exerting a beneficial effect.

Pearl and his coworkers reported long term improvement in symptoms in 5 of 6 patients treated with long acting nitrates[86]. Other authors have noted the persistence of a

beneficial effect on the PVR and CI after 3 to 8 months of therapy with oral hydrallazine[67, 102]. Nifedipine has been shown to effect an improvement in pulmonary haemodynamics which persisted after 14 months of therapy[12,27,101] while isoprenaline has had a similar effect up to 47 months in suitable patients[85,88]. Two groups of investigators have shown that diazoxide continues to exert a beneficial effect on the pulmonary vasculature after 6 to 8 months[58,125]. A continuous infusion of prostacycline for 13 months achieved a satisfactory result in one patient[45].

The most common response to vasodilator therapy in general is a decrease in PVR and an increase in CO with no significant change in PAP. The reduction in PVR achieved by some agents is thought to be secondary to an increase in CO[125]. However, studies in dogs have shown that isosorbide dinitrate decreased PVR when CO was maintained constant by bypassing either the right or the left ventricle[89].

Hermiller et al reported that isosorbide dinitrate was the only one of 6 vasodilators tested to achieve a significant reduction in PAP[44]. Our study confirmed that isosorbide tended to be more effective in reducing pulmonary artery pressure than the other agents evaluated.

However, merely decreasing PVR without reducing PAP may be beneficial to the patient. Several studies have shown an inverse relationship between PVR and survival with the PAP itself having little effect on prognosis[39,93,99]. Rubin

and his colleagues reported that nifedipine increased right ventricular ejection fraction and reduced end diastolic volume measured by radionuclide angiocardiography when PVR was significantly reduced although pulmonary artery pressures remained relatively unchanged[101]. In addition there is often an improvement in symptoms associated with the increase in cardiac output achieved by vasodilator therapy[12,67,101].

In general, our experience with vasodilator therapy in the management of PPH has been less encouraging than some reports by other authors[12,67,102,125]. A similar lack of significant effect was shown by Hermiller and his colleagues[44], and a beneficial effect of vasodilator therapy on overall mortality has not as yet been shown[39,93]. Reliable assessment of both short and long term effects of vasodilator therapy is complicated by a marked spontaneous variability in PVR from hour to hour in these patients[94] and by occasional spontaneous regression of the condition[99]. In spite of this, there is sufficient evidence to show that there is indeed a subgroup of these patients in which long term vasodilator therapy is effective in achieving symptomatic and haemodynamic improvement.

VIII E(v): Heart-lung transplantation.

Only one patient underwent heart-lung transplantation during the period of this study. No haemodynamic studies were performed post-operatively, but she was symptomatically improved. The subsequent development of chronic rejection and persistent pulmonary tuberculosis necessitated repeat transplantation one year later.

After performing 28 heart-lung transplants during the course of $4^{1}/2$ years the Stanford group point out that because of the uncertainties associated with this form of therapy at present it should not yet be undertaken as a routine clinical procedure[10]. They attempt to select patients who have limiting symptoms and who are expected to live only one or two years more without surgery. Actuarial survival curves based on their data predict 1 and 2 year survial rates of 71% and 57% respectively[25]. Previous authors have attempted to define criteria to enable identification of the PPH patient with a poor prognosis who would be a suitable candidate for heart-lung transplantation[39,93,99]. We have attempted to identify features associated with short and long term survival in our patient group. Our findings are expressed in the next section.

VIII F: Features of short and long term survivors.

Seven patients with full haemodynamic evaluation and complete follow up died within 12 months of initial catheterization. These constituted the short survival group. A similar number who survived 40 months or longer from initial evaluation constituted the long survival group. The demographic and clinical features of the 2 groups are outlined in Table VIII F[i].

Table VIII F[i]: Demographic and historical features of short and long survival groups.

	Short survival group (<12 mths)	Long survival group (>40 mths)	P
Number	7	7	
Age (years)	25.7 ±12.5*	35.3±11.5*	
Duration of symptoms (months)	18.9±15.8*	44.5±60.3*	
Sex: males females	43% 57%	0% 100%	
Race: Black White Coloured	0% 43% 57%	0% 71% 29%	
Associated connective tissue disease	0%	0%	
Dyspnoea on exertion	100%	86%	
NYHA Grade	2.8±0.8*	2.6±0.8*	
Chest Pain	29%	43%	
Vertigo/syncope	43%	57%	
Raynaud's phenomenon	14%	17%	
Smoking	50%	50%	
Previously pregnant (% of females)	25%	100%	<0.05
Number of pregnancies	1.5±3	1.8±0.8*	
Oral contraception (% of females)	33%	60%	

* = MEAN ± SD

There was no significant difference between the age of onset of the disease in the 2 groups. This lack of correlation between age of onset and prognosis has been noted in previous studies[39,99]. As paediatric patients are not seen at our clinic our study group did not include children. However, the 3 patients under the age of 15 years who were included all died within 3 years of the onset of symptoms. Fuster and his colleagues found that 64% of their patients who were 14 year old or younger died during the first year of follow up[39]. This led them to postulate that younger patients with PPH do badly, but as their group of younger patients was relatively small this apparent difference in survival was not statistically significant.

Sex was not a factor influencing prognosis. Fuster and his coworkers noted the same finding[39] whereas Rich and Levy noted a larger proportion of females among their non survivors[93]. One of our patients fell pregnant but this did not have any adverse effect on her clinical or haemodynamic status. This observation is in conflict with a previous report that pregnancy worsens the prognosis of patients with PPH. The mean survival after pregnancy was reported to be less than 5 years[69]. However, this assertion was challenged by the finding of Rozkovec et al. that pregnancy at the time of diagnosis seemed to be a favourable prognostic factor[99]. All five of their cases who presented in late pregnancy or after delivery had prolonged survival. Spontaneous improvement occurred in 2. They postulated that the stress of pregnancy might have

induced the onset of symptoms at an earlier stage of the disease process and that there might have been an element of pregnancy induced vasoconstriction which reversed after delivery. A significantly larger proportion of females in our long survival group had been pregnant at various periods prior to the onset of this condition. The rate of progression of the condition may slow when these pregnancy related hormonal stimuli are removed resulting in a better prognosis than other forms of PPH in which non-hormonal factors may play a more significant causative role.

There was no significant difference between other demographic features and the nature and duration of symptoms of the two groups.

Table VIII F[ii]a: Clinical, chest radiographic and electrocardiographic features of the short and long survival groups.

	Short survival group (< 12 mths)	Long survival group (> 40 mths)	P
Clinical signs:			
Elevated JVP	71%	67%	
Mean JVP	6.4±4.5*	4±3.7*	
Accentuated P_2	100%	86%	
Right ventricular heave	100%	86%	
Tricuspid incompetence murmur	43%	14%	
Pulmonary incompetence murmur	43%	29%	
RVS_3	29%	57%	
RVS_4	14%	29%	
Hepatomegaly	0%	29%	
Peripheral oedema	29%	0%	
Cyanosis	29%	14%	
Chest radiograph			
Cardiomegaly	86%	57%	
Dilated proximal pulmonary arteries	100%	86%	
Peripheral pruning	50%	43%	
Electrocardiograph features			
Right ventricular hypertrophy	100%	43%	<0.05
Right ventricular strain	86%	43%	
Right axis deviation	100%	86%	
Right atrial enlargement	50%	14%	
Right bundle branch block	17%	29%	

* = mean ± SD

The clinical and chest radiographic features of the two groups were not significantly different.

All of the patients in our short survival group had electrocardiographic evidence of right ventricular hypertrophy. This feature occurred significantly less frequently in the long survival group.

Table VIII F[ii]b: Comparison of clinical, chest radiographic and electrocardiographic features of short and long survival groups in this study and that of Rozkovec, Montanes and Oakley[99] (% of patients).

Feature	Study	Short survival	Long survival	"p"
Clinical features	Chapman			NS
	Rozkovec			NS
ECG				
Right ventricular hypertrophy	Chapman	100	43	<0.05
	Rozkovec	100	83	NS
Right axis deviation	Chapman	100	86	NS
	Rozkovec	100	66.6	<0.05
Right atrial enlargement	Chapman	50	14	NS
	Rozkovec	94.4	25	<0.0005
Chest X-Ray				
Right ventricular enlargement	Chapman	86	57	NS
	Rozkovec	100	66.6	<0.01

Apart from a higher prevalence of radiographically apparent right ventricular enlargement in their short survival group, the findings of the Hammersmith group in this regard were similar to our own (Table VIII F[ii]b).

Although features of right ventricular hypertrophy were also noted in all patients in the short survival group in the study by Rozkovec et al[99], this was not significantly different from the prevalence of this feature in the groups with a longer survival. Right axis deviation and right ventricular strain pattern occurred significantly more frequently in their short survival group. The prevalence of these features in our short survival group although somewhat higher than in the long survival group was not significantly so.

Table VIII F[iii]a: Pulmonary angiographic and haemodynamic features of the short and long survival groups.

	Short survival group (< 12 mths)	Long survival group (> 40 mths)	P
Pulmonary angiogram			
Proximal dilatation	66%	57%	
Main or several lobar pulmonary artery defects	0%	0%	
Small vessel occlusion	67%	57%	
Haemodynamic parameters (Mean + SD)			
PAP, mmHg	83.6±20.1	60.6±14.3	<0.05
PVR, units	25.4± 9.7	13.1±8.8	<0.05
SVR, units	25.8± 6.8	21.7±8.8	
CI, C $min^{-1}m^{-2}$	2.1±0.5	2.7±1.2	
RAP, mmHg	8.8±5.9	8.9±6.2	

PAP = Mean pulmonary artery pressure

PVR = Pulmonary vascular resistance

SVR = Systemic vascular resistance

CI = Cardiac index

RAP = Mean right atrial pressure

There was no significant difference between the pulmonary angiographic features of the short and long survival groups. The PAP and PVR were significantly higher in the short survival group. Other authors have failed to show a significant relationship between survival and the degree of pulmonary hypertension although their longer surviving patients tended to have slightly lower pulmonary artery pressures (Table VIII F[iii]b). These authors have noted a

significantly higher PVR in their short survival groups. Fuster and his colleagues found systemic arterial oxygen saturation to be a good predictor of survival ($p<0.00001$)[39].

Table VIII F[iii]b: Comparison of haemodynamic parameters of short and long survival groups in this study and those of Rozkovec, Montanes and Oakley[99] and Rich and Levy[93].

Parameter	Study	Short survival	Long survival	"p"
PAP, mmHg	Chapman	84	61	<0.05
	Rozkovec	64	61	NS (i vs ii)
	Rich & Levy	74	53	NS
PVR, units	Chapman	32	13	<0.05
	Rozkovec	21	12	<0.005 (i vs iii)
	Rich & Levy	57	20	<0.01
SVR, units	Chapman	27	21	NS
	Rozkovec	28	19	<0.01
	Rich & Levy	64	43	<0.05
CI, $lmin^{-1}m^{-2}$	Chapman	2.1	2.7	NS
	Rich & Levy	1.2	2.3	<0.01
RAP, mmHg	Chapman	9	9	NS
	Rich & Levy	17	6	<0.01

Both previous studies noted a significantly lower mean cardiac index in their short survival group but the trend towards a lower mean cardiac index in our short survival group did not attain statistical significance. Mean right atrial pressure was significantly higher in Rich and Levy's short survival group (17 vs 6 mmHg; $p<0.01$). However, neither we nor Rozkovec and his colleagues noted any significant difference between the two groups with respect to this parameter. Although no significant difference in SVR

existed between the two groups in our study, both Rich and Levy and the Hammersmith group reported a significantly higher mean SVR in their short survival group.

Rozkovec and his colleagues noted that a patent foramen ovale was associated with a longer survival and postulated that such a shunt permitted adequate left ventricular filling at times of increased demand and prevented sudden death[99]. Only one of our patients had a patent foramen ovale. It did not appear to confer any protective benefit on her as she died within 15 months of the onset of symptoms.

We were unable to compare the responsiveness to vasodilators in the 2 groups as too few of these patients with adequate follow up were tested to enable any meaningful conclusions to be drawn. However, Rich and Levy noted no difference in the acute response to vasodilator therapy between the short and long survival groups[93].

Various authors have sought to define criteria to enable prediction of survival of the individual patient. Such criteria would be of enormous assistance to the attending physician in evaluating the advisability and timing of such aggressive therapeutic options as heart-lung transplantation. Analysis of the haemodynamic parameters measured at diagnosis in the short and long survival groups in relation to survival time from presentation by means of Spearman's rank correlation failed to show a relationship. This was limited by the fact that not all haemodynamic data was present for

all patients. Rich and Levy found that the stroke volume index was the best single predictor of survival, with a figure of less than 17 ml/beat/m^2 associated with a poor prognosis. Only one of our short survival group had a stroke volume index calculated. The figure of 20 ml/beat/m^2 in this patient does not entirely support the findings of Rich and Levy, but it was certainly considerably lower than the mean of 43 ml/beat/m^2 in the long survival group. Right atrial pressure was the best measured predictor of survival in their study, with a right atrial pressure of greater than 10mmHg also predictive of a poor prognosis. The mean right atrial pressure in our two groups, however, was similar. They found cardiac index, pulmonary vascular resistance and pulmonary artery pressure to be relatively poor predictors of prognosis[93].

Rozkovec and his colleagues noted that cardiac output was directly related to survival and that there was an inverse relationship between duration of survival and PVR, SVR and left ventricular end diastolic pressure. Systemic and pulmonary arterial and right atrial pressure did not correlate with survial[99].

Univariate analysis of various haemodynamic variables by Fuster et al revealed that pulmonary and systemic arterial oxygen saturation and total pulmonary resistance were the most strongly predictive of early death. The 3 year survival was 55% among patients whose pulmonary arterial oxygen saturation was 63% or higher while it was 17% in those in

whom it was lower[39]. Stepwise multivariate analysis identified that pulmonary arterial oxygen saturation and anticoagulant therapy were the only two variables of prognostic significance. We did not measure pulmonary arterial oxygen saturation but found a significant difference in systemic arterial oxygen saturation between our short and long survival groups.

There are as yet still no adequate criteria by which individual patients can be categorized prospectively into specific prognostic groups at the time of initial evaluation. Our study is the first to show a significantly higher mean pulmonary artery pressure in a short survival group. No patient with a mean pulmonary artery pressure of 75 mmHg or greater survived for longer than 12 months.

IX: CONCLUSION

This study has analysed the features and progress of 38 patients with PPH over a period of 28 years at Groote Schuur Hospital.

The first aim of the study was to analyse the clinical features of these patients and to compare them with the features of a group of patients with TPH. The greater prevalence of Raynaud's phenomenon in the PPH group confirms previous reports[122,123] and suggests the existence of a common mechanism causing spasm of both the pulmonary and digital arterioles[35]. The PPH group was younger and had a right ventricular fourth heart sound detected more frequently. A similar proportion of the females in the two groups had previously been pregnant but each mother in the TPH group had delivered significantly more children. While the association of pulmonary thromboembolism with pregnancy is well recognised[18], certain authors have postulated that pregnancy or the administration of female hormones also plays a role in the pathogenesis of primary pulmonary hypertension.

The clinical features of the two groups were similar apart from the absence of a clinically detectable fourth heart sound and a higher prevalence of lower extremity varicosities in the TPH group. The PPH group had a significantly higher prevalence of electrocardiographic evidence of right axis deviation and right ventricular hypertrophy. Chest radiographic features were similar in both groups.

Although all patients with total lung capacity below two-thirds predicted were excluded in an attempt to eliminate restrictive lung disease contributing to the pulmonary hypertension, the mean value of this parameter in this study was well below predicted and significantly lower than that found in the TPH group. Similar findings have been reported previously.[9,47,107] The physiological mechanism responsible for the restrictive ventilatory pattern has not yet been defined. Clarification of the frequency with which this occurs awaits a study in which interstitial lung disease is histologically excluded in all patients in the study group.

As none of the PPH patients who were subjected to lower limb venography showed a positive result whereas over half of the patients in the TPH group had evidence of thrombus, a positive venogram in this clinical setting appears to be fairly strong evidence in favour of a diagnosis of TPH.

Pulmonary artery pressure was significantly higher in the PPH group. A similar trend noted by D'Alonzo and his colleagues did not attain statistical significance.[23] The role of pulmonary angiography or open lung biopsy in distinguishing these two entities is controversial.[79] Surgery and pulmonary angiography have been reported to have a greatly increased risk in patients with pulmonary hypertension[26,114,126]. Other authors have reported no increased risk associated with open lung biopsy in such

patients.[12] We do not routinely perform open lung biopsy and prefer to use pulmonary angiography to clarify the diagnosis. No untoward effects of pulmonary angiography were noted during this study. The recent introduction of non-ionic contrast medium is expected to reduce the risk associated with pulmonary angiography even further. Radionuclide lung scanning proved a safe and effective non-invasive means of distinguishing between these two conditions.

The second aim of the study was to evaluate the prognosis of these patients. Fifty-four percent of the PPH group survived 40 months or more from onset of symptoms. As the TPH group was relatively small, the trend towards a better survival at 40 months than in the PPH group was not statistically significant. Within the PPH group a trend towards a worse prognosis in patients with associated connective tissue disease did not attain statistical significance. Although repeat haemodynamic studies have not been performed, it appears clinically that in 2 PPH patients the disease progression has halted while 2 further patients have shown an improvement of symptoms and exercise tolerance suggestive of regression of the disease.

The third aim of the study was to assess the efficacy of various therapeutic strategies in the PPH patients. The trend towards a better 40 month survival in patients on long term oral anticoagulants did not reach statistical significance. We were unable to identify a group of patients

who consistently responded to the various vasodilators tested: different agents showed different degrees of effectiveness in different patients. Severe side effects prompting cessation of long term vasodilator therapy occurred in 3 of the 6 cases in whom it was attempted. A beneficial effect appears to have occurred in two patients. There appears to be a small group of patients in whom such therapy is effective. One patient underwent heart-lung transplantation. Twelve months later she was still alive but had undergone repeat transplantation because of chronic rejection. Actuarial survival curves predict one and two year survival rates after heart-lung transplantation of 71% and 51% respectively[25]. Only those patients with a severe progressive form of the disease should be considered for surgery.

The fourth aim of the study was to identify factors predictive of the outcome of PPH. Neither clinical nor chest radiographic features were indicative of prognosis. Electrocardiographic evidence of right ventricular hypertrophy was significantly more common, while mean pulmonary artery pressure and pulmonary vascular resistance were higher in the short survival group. However the wide range of values within both groups of the parameters measured makes accurate prediction of survival for the individual patient extremely difficult. No correlation was found between initial haemodynamic parameters measured at diagnosis and survival in the short and long survival groups . Previously proposed criteria for prediction[93] have not been

confirmed by other studies[99]. The assessment of the prognosis of an individual patient requires careful correlation of all clinical and haemodynamic data gathered at the time of diagnosis with assessment of the rate of progression by means of regular clinical re-evaluation. The recently developed technique of non-invasive assessment of pulmonary artery pressure[21] promises to be of value in following these patients and assessing the stage of the disease at which heart-lung transplantation offers a better prognosis than conservative treatment.

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